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Validation of Peripheral Artery Disease Quality of Life Questionnaire (PADQoL) and Measuring Disease-specific Quality of Life among Patients with Peripheral Artery Disease

Ph.D. Thesis

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ABBREVIATIONS

ABI	Ankle-Brachial Index
APAD	Asymptomatic Peripheral Artery Disease
BMI	Body Mass Imdex
CHD	Chronic Heart Disease
CI	Confidence Interval
CLI	Critical Limb Ischaemia
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation strategies
COPD	Chronic Obstructive Puémonary Disease
CV	Cardiovacular
CVD	Global Burden of Disease Cardiocascular disease
DALY	Disability Adjusted Life Years
DASH	Disabilities of the Arm, Shoulder and Hand
EMR	Eastern Mediterranean Region
ESC	European Society of Cardiology
ESP	European Standard Population
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
EuroQoL-5D	European Quality of Life 5 Dimensions
EUROSTAT	European Statistics Comission
GBD	Global Burden of Disease
HICs	High-Income Countries
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HUNVASC DATA	Hungarian Vascular Data
KMO	Kaiser-Meyer-Olkin
LEAD	Lower Extremity Peripheral Artery Disease
LMICs	Low-Income and Middle-Income Countries
MACE	Major Adverse Coronary Event
MALE	Major AdverseLimb Event
MI	Transient Ischemic Attack Myocardial Infarction
NCDs	Non-communicable Diseases
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PADQoL	Peripheral Artery Disease Quality of Life
PANDORA	The Prevalence of peripheral Arterial disease in subjects with a non-high cardiovascular disease risk, with No overt vascular Diseases nOR diAbetes mellitus study
PAOD	Peripheral Artery Occlusive Disease
PROMs	Patent Reported Outcomes Measures
SD	Standard deviation
SF-36	Short-form 36
SL	Source Language
T1	Forward Translation 1

T2	Forward Translation 2
T3	Forward Translation 3
TASC	Trans-Atlantic Inter Society Consensus
TIA	Transient Ischemic Attack
TL	Target Language
UN	United Nations
USA	United States of America
VASCUNET	Vascular Network
VASQUQOL	Vascular Quality of Life
WELCH	Walking Estimated-Limitation Calculated by History
WHO	World Health Organization
WIfI	Wound Infection Ischaemia
WIQ	Walking Impairment Questionnaire
WPR	Western Pacific Region
YLD	Years Lived with Disability
YLL	Years of Life Lost

1. INTRODUCTION

Peripheral artery disease (PAD) is the progressive narrowing or blockage of the arteries in the legs or lower extremities also indicating generalised atherosclerosis. Risk factors mainly include diabetes mellitus and smoking, and PAD is associated with significant CVD morbidity and mortality. While some patients remain asymptomatic for a period of time, typical symptoms of PAD may range from atypical exertional pain to severe ischaemic pain at rest. If untreated PAD may result in tissue loss, minor or major amputations. The disease severely impacts quality of life including physical functioning (mainly walking), and consequently, emotional and social life (1, 2, 3, 4, 5). A considerable number of affected patients develop depression (6, 7). Due to global populations moving towards an older age spectrum, past decades have witnessed marked increase in the disease burden associated with atherosclerotic cardiovascular diseases (CVDs) worldwide. Despite considerable advances in medical technologies and pharmaceutical treatment modalities, the prevalence of PAD is constantly increasing with more than 230 million people estimated to be living with PAD (8). PAD and diabetes are the major causes of lower limb amputations throughout the world with our country, Hungary, sadly showing very high amputation rates and low post-amputation survival (9, 10). The associated disease burden on health care systems is threrefore, considerable (11, 12, 13). Disease awareness continues to be surprisingly low (14, 15, 16, 17). Health-related quality of life has gained more importance in clinical studies, primarily, with the use of generic and disease-specific questionnaires. While generic tools are designed to measure quality of life from more general aspects of health status, disease specific quality of life questionnaires are developed and constructed to assess quality of life in certain subpopulations, in patients suffering from a particular disease, or prior to and after particular therapeutic interventions (18, 19, 20). Although clinical outcome measures in PAD including walking capacity (e.g., treadmill testing), physiological measurements such as the ankle-brachial index (ABI), patency tests of revascularized segments, or amputation-free survival provide an adequate and clear picture of the patients' objective clinical status, HRQoL measures, patient reported outcomes tools have been proven to add valuable information about the actual daily functioning of PAD patients. To assess quality of life in this patient population, we initially set out to linguistically validate and cross-culturally adapt the PADQoL disease-specific questionnaire (21). PADQOL was developed by Treat-

Jacobson and colleagues with the aim to provide a novel tool for the assessment and evaluation of the impact of PAD on health-related quality of life (HRQoL) with special focus on the subjective, psycho-social burden of the disease besides limitations in physical functioning (22). Due to an increase in the number of multinational and multicultural research projects, the translation and cultural adaptation of health status measures is strictly regulated by internationally applied protocols according to which the process we followed included: two initial translations, synthesis of the two translations, backward translations and expert committee assessment to compare translations and create the pre-final version, and pilot-testing of the pre-final version (21, 23).

2. AIMS

The aim of our study was to perform the linguistic validation and cross-cultural adaptation of the Peripheral Artery Disease Quality of Life (PADQoL) disease-specific questionnaire into Hungarian, and subsequently, to assess and evaluate disease-specific quality of life among Hungarian patients suffering from various stages of peripheral artery disease. We also intended to research and thereby, provide an up-to-date overview on the epidemiology of peripheral artery disease from a global, international and national perspective.

Main aims of the thesis are summarised as follows:

1. To research the epidemiology of peripheral artery disease and provide an up-to date review from a global, international and national perspective, with special focus on the Hungarian situation.
2. To perform the linguistic validation and cross-cultural adaptation of PADQoL disease-specific quality of life measure through the following stages: forward translation, consensus version, back translation, consensus meeting, pre-final Hungarian version of PADQoL.
3. To perform the pilot testing of the pre-final Hungarian version of PADQoL via conducting cognitive interviews with patients living with PAD (n=30), and thereby, to create the final Hungarian version of the questionnaire.
4. To investigate HRQoL among PAD patients in Hungary using the validated Hungarian version of the PADQoL questionnaire. Our cross-sectional study aimed to assess HRQoL among patients living with different stages of PAD with special focus on the associations between more advanced stages of PAD (Fontaine III and IV) and HRQoL including different areas of social life, mobility, and emotional health.

3. EPIDEMIOLOGY OF PERIPHERAL ARTERY DISEASE: NARRATIVE REVIEW [1]

Past decades have witnessed a major epidemiologic transition with a considerable increase in the disease burden associated with atherosclerotic cardiovascular diseases (CVDs), with low-income and middle-income countries (LMICs) experiencing substantial increase in CVDs. As the global population is aging and peripheral artery disease (PAD) is strongly age-related, it is estimated to become increasingly prevalent in the future. PAD shares risk factors with coronary and cerebrovascular diseases, particularly diabetes mellitus and smoking, and is associated with significant CVD morbidity and mortality. Despite advances in therapeutic modalities, 236 million people were estimated to be suffering from PAD worldwide in 2015, and numbers have been rising since. The prevalence of asymptomatic PAD has remained high; PAD prevalence seems higher among women and is related to ethnicity. Although several epidemiological studies have been published on PAD during the past decades, data from LMICs are scarce. Besides providing up-to-date epidemiological data retrieved from the literature and the Global Burden of Disease (GBD) study database, this narrative review also intends to draw attention to the substantial disease burden of PAD manifesting in more Years of Life Lost (YLL), age-adjusted mortality and amputation rates, with a special focus on some European countries and especially Hungary, the country with the highest amputation rate in Europe.

[1] *The chapter is based on the article:*
***Horváth L**, Németh N, Fehér G, Kívés Zs, Endrei D, Boncz I. Epidemiology of Peripheral Artery Disease: Narrative Review. Life. 2022; 12(7): 1041. https://doi.org/10.3390/ life12071041*

Introduction

Noncommunicable diseases (NCDs) have emerged as leading causes of morbidity and mortality in developed and developing regions of the world. The disease burden attributed to NCDs continues to increase worldwide, with cardiovascular diseases (CVDs) the leading cause of mortality and morbidity. Consequently, the prevalence of peripheral artery disease (PAD), also called lower extremity peripheral artery disease (LEAD), has been rising markedly [1, 2, 24]. PAD is a progressive atherosclerotic disease of the lower extremities and is considered an indicator of generalised atherosclerosis [3, 4, 25]. The most common symptom of PAD is claudication, cramping pain in the calves, thighs or buttocks, characteristically triggered by walking and subsiding with rest. Further symptoms may also include atypical pain on exertion and ischaemic pain at rest. The final stages may result in tissue loss and amputation. PAD may remain asymptomatic for a while, but symptomatic PAD is associated with severe limitations in physical function, especially walking and a wide range of daily activities [5, 26, 27, 28]. A large majority of patients remain asymptomatic even with an ABI > 0.9. Asymptomatic Peripheral Artery Disease (APAD) combined with traditional risk factors (hypertension, diabetes mellitus and smoking) substantially elevates cardiovascular (CV) risk. Patients with suspected underlying disease should undergo further noninvasive tests [29, 30]. PAD has been shown to be associated with significant morbidity and mortality from cardiovascular disease (CVD), myocardial infarction (MI), stroke and major adverse coronary events (MACE). Patients suffering from PAD have been found to have an equal risk of a subsequent stroke or MI as patients with coronary artery disease [31, 32]. Individuals with early-stage PAD either do not experience or frequently under-report claudication symptoms (pain in the lower extremities) and despite the high in-hospital costs associated with advanced stage PAD, the disease often remains undetected and untreated [33, 34, 35]. A recent systematic review has revealed an estimated increase in PAD prevalence of more than 17% (30 million people) over a period of 5 years (2010–2015) from previous estimates of 202.06 million people suffering from PAD globally. In 2015, around 236 million people were estimated to have PAD globally, with a slightly higher percentage of women affected [8, 36]. Regardless of advances in treatment modalities, outcomes have remained suboptimal not only in low- and middle-income countries but in countries with higher socioeconomic status as well, especially in patients with critical limb ischaemia (CLI) [37, 38]. The number of PAD patients has been markedly increasing, resulting in an increase of related

disease burden upon healthcare systems worldwide [11, 12, 13]. Symptomatic PAD is associated with marked changes in quality of life. PAD and diabetes are the major causes of lower limb amputations throughout the world [25, 39]. Women are equally affected by the burden of PAD and frequently experience faster decline in quality of life and functional capacity than men, with minority women often having worse outcomes than white women [40]. Awareness of the disease is still strikingly low among at-risk populations and the general population as well [14, 15, 16,17]. Besides the significant reduction in quality of life, a considerable number of patients with PAD develop symptoms of depression. Depressive symptomatology among affected patients has been associated with limitations in physical functioning [6, 7]. The treatment of PAD requires a multidisciplinary approach, addressing two primary aspects: specific symptoms and the risks and complications a specific lesion could potentially lead to, and reducing CV risk of these patients. Non-pharmacological measures are also crucial and may significantly contribute to reducing CV risk, including smoking cessation as the most important element of lifestyle modification, together with a healthy diet and regular physical exercise. [5, 41]. Supervised exercise programmes have been shown to be beneficial for patients with symptomatic PAD in terms of walking ability, functional status and health-related quality of life (HRQoL) [42]. According to current guidelines, pharmacotherapy for PAD patients should include antiplatelet therapy and statin agents, taking into consideration additional risk factors such as diabetes mellitus or hypertension. Glycaemic control and antihypertensive therapy are vital in reducing the incidence of future CV events in symptomatic PAD patients. Choosing the optimal antithrombotic regimen to reduce ischaemic cardiac and limb events without increasing the risk of major and life-threatening bleeding has been a challenging and extensively studied issue given the heterogeneity of PAD patients [43, 44]. A recent analysis of the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial showed increasing frequency of ischaemic cerebrovascular events over time in this population, which underlines the importance of PAD as a potential risk factor of stroke and transient ischaemic attack (TIA) [29]. The aim of our review is to provide an in-depth overview of the topic to gain up-to-date information about the prevalence, risk factors, consequences, and burden of this phenomenon a stroke physician should be aware of. We also discuss the situation of PAD management in Hungary, a country performing at the lower end of the spectrum with regard to prevention, treatment and amputation rates. We performed a narrative review. A literature search was conducted using the Medline Pubmed database with the following search terms: peripheral artery disease, epidemiology,

prevalence, mortality and years of life lost. Two experts screened the abstracts and identified the most relevant papers. Primary data were extracted from the global burden of disease (GBD) study [1]. The GBD database was accessed through the internet from www.healthdata.org provided by the Institute for Health Metrics and Evaluation [45].

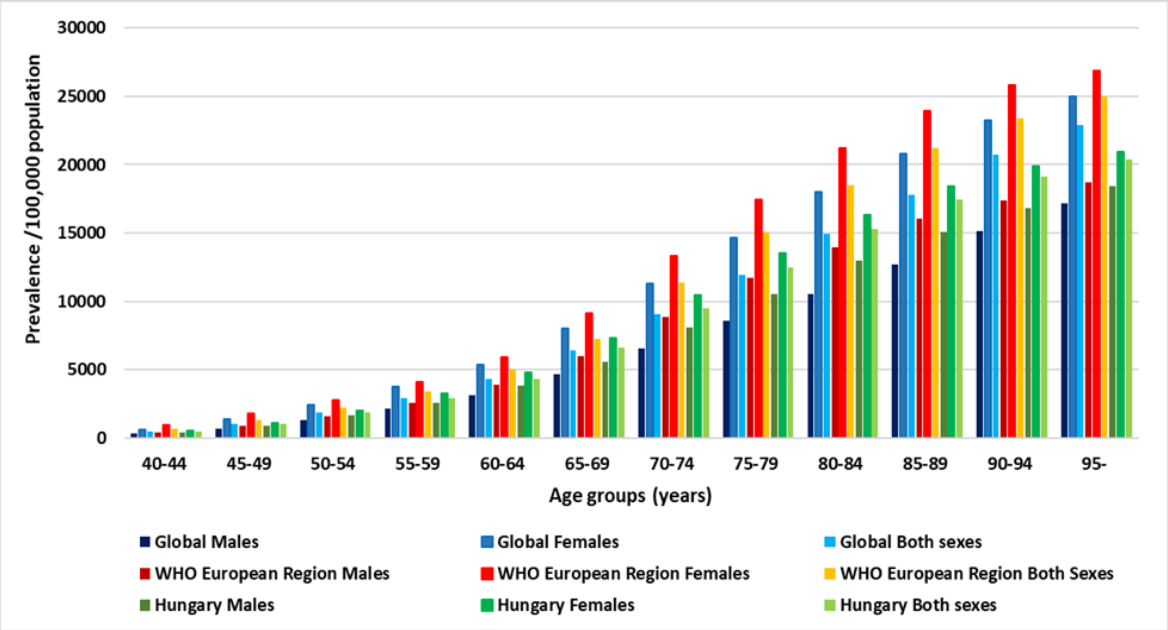
2. PAD Prevalence Worldwide

The 20th century witnessed dramatic advancements in the history of healthcare and medicine resulting in the so-called 'epidemiologic transition'. Industrialisation and urbanisation resulted in a shift in major causes of morbidity and mortality, primarily in societies with more advanced socioeconomic status, from nutritional deficiencies and infectious diseases towards degenerative chronic diseases e.g., cardiovascular diseases, cancers and diabetes. The epidemiologic transition has not ended; different global regions, countries or even subgroups of a given country's population are undergoing different stages of the process. As a consequence of the above phenomenon, from among noncommunicable diseases, atherosclerotic CVD has become a global epidemic accounting for alarmingly high mortality rates. Countries that have been successful in their efforts to prevent, diagnose, and treat cardio and cerebrovascular diseases have had to face the problems posed by an aging society upon their healthcare systems [2]. The epidemiology of PAD has been studied more extensively in Western countries since the last decade of the twentieth century, resulting in comprehensive descriptions of the disease, its aetiology, prevention and therapeutic modalities. The increasing global burden of CVDs and other NCDs in LMICs mandated epidemiological data to be updated and thus to provide a clearer picture of the immensity of the problem societies and healthcare systems have to tackle [1, 2, 24]. Despite LMICs having been mostly impacted by the epidemiological transition, epidemiological studies from these countries are still scarce. It was the Global Peripheral Artery Disease Study that first established the global and regional prevalence of PAD in the general population using the ankle-brachial index (ABI; the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm) of 0.90 or less as a diagnostic tool and estimated the prevalence of PAD to be around 202 million worldwide in 2010 with approximately 70% of the affected population living in LMICs [8]. An updated systematic review and analysis studied the prevalence of PAD in the general population at global, regional and national levels. ABI $\leq$ 0.9 was used as an indicator of disease. Age-specific and sex-specific prevalence of PAD was compared in high-income

countries (HICs) and low-income and middle-income countries (LMICs). Authors used United Nations (UN) population data to generate the number of people suffering from PAD in 2015. According to the review, there was a slightly higher prevalence in LMICs than in HICs (4.32% vs. 3.54% at 40–44 years) among younger individuals; nevertheless, HICs witnessed greater increase with age, resulting in a higher prevalence in HICs than LMICs at older ages (21.24% vs. 12.04% at 80–84 years). Regarding sex differences, LMICs showed little difference between men and women (e.g. 6.40% vs. 6.37% at 55–59 years). The study estimated an overall, global prevalence of PAD in the population aged 25 years or above to be 5.56%, with a higher estimated prevalence in HICs than in LMICs (7.37% vs. 5.09%) which meant an estimated total number of 236.62 million people aged 25 years and older suffering from the disease in 2015 worldwide, with 72.91% living in LMICs. Women were slightly more affected, accounting for 52.23% of the PAD population. Authors identified smoking, diabetes, hypertension, and hypercholesterolaemia as major risk factors of PAD. Among all WHO regions, the Western Pacific Region (WPR) had the highest number of PAD cases (74.08 million), and the Eastern Mediterranean Region (EMR) was found to have the lowest case numbers (14.67 million) globally. The prevalence of PAD was the highest in the European Region (7.99%) with the age group 45–54 years being mostly responsible for high case numbers. Prevalence was the lowest in the African region (4.06%). Fifteen countries had case numbers accounting for more than two thirds (68%) of the global prevalence, with China, India and the USA having reported the highest case numbers [36]. Studies from the USA revealed high mean, annualised prevalence of PAD (10.69%) and CLI (1.33%) among Medicare and Medicaid beneficiaries [46]. Higher age-standardised incidence and prevalence was found in the black population especially among black women compared with the white population. A recent systematic review and meta-analysis also highlighted the nearly twice as high mean prevalence of PAD among the general population for black people (6.7%) compared to white and Asian populations (3.5% and 3.7% respectively), emphasizing existing racial disparities within the American population and the need for more comprehensive and extensive prevention programmes [47]. Another systematic review also found higher PAD rates among women in general compared to men (3.8% vs. 3.2%), especially in the diabetic population in the USA (13.7% vs. 10%) [48]. Studies from Europe have also revealed a rapid increase in the prevalence of PAD in the European region. From previous estimates of 5.3% of the population living with the disease in 2010, which meant 40 million individuals living with PAD from among the 750 million inhabitants a decade ago, a later

study gave estimates of around 50 million having PAD in the European region in 2015, with around 33 million living in HICs [8, 36]. The PANDORA study including 10,287 patients highlighted significant variations in PAD prevalence in Europe, with Greece having the highest prevalence (28.0%), followed by Italy (22.9%), France (12.2%), Switzerland (12.2%), the Netherlands (8.1%) and Belgium (7.0%) [49, 50]. Early studies from Northern Europe established the high prevalence of PAD among the elderly (19.1% in the Netherlands, 18% in Sweden) and called attention to the fact that the vast majority of PAD patients remain asymptomatic [4, 30, 37]. Asymptomatic PAD and CLI were more prevalent among women (12.6% vs. 9.4%; 1.5% vs. 0.8% respectively) [37]. Incidence and prevalence were found to be strongly affected by age and PAD prevalence was higher among women. Asymptomatic PAD was found to be associated with age, smoking status, hypertension and diabetes. CLI was found in around 1% of study populations [4, 32, 37]. In 2019, according to Global Burden of Disease (GBD) data retrieved from vizhub. healthdata.org [45], the global prevalence of PAD per 100,000 population was 332.32 in males and 621.11 in females in the 40–44 age group and increased markedly with age, resulting in prevalence rates of 17,195.57 in males and 24,965.3 in females aged 95 and older. The WHO European region showed similar rates with a prevalence of 407.1 among males and 940 among females aged 40–44, and significantly increased rates of 18,664.74 in men and 26,896.52 in women aged 95 years and above. As for Hungary, in 2019, PAD was less prevalent among males than among females with a rate of 443.83 at the age 40–44 years increasing up to 18,448.15 by age 95. In women, prevalence rates were higher compared to the above rates with 529.86 in the 40–44 age group, and 20,962 in women aged 95 and older. Females showed overall higher prevalence rates in all age groups, which corresponds with findings of earlier studies and stressing a need for action targeting the female population. Generally, PAD prevalence shows marked increase with age especially above age 65 years **(Figure 1)**.

Figure 1. Prevalence of PAD per 100.000 population by age group in males, females and both sexes combined, in 2019.
(graph by authors, source: https://vizhub.healthdata.org).



3. Mortality Attributed to PAD

It is often argued that mortality statistics are of limited usefulness with respect to PAD, as the majority of these patients die from coronary heart disease, stroke or cancer and thus the cause of death is identified as such. A very small minority die of PAD only and consequently, mortality statistics may not provide clear insights in this respect [51]. A systematic review analysing randomised and observational studies between 2003–2017 revealed pooled event rates for all-cause and CVD mortality, MI, stroke, MACE, and major amputation as 113, 39, 20, 12, 71 and 70 per 1000 person-years, respectively, among PAD patients. Patients with CLI were identified to be at the highest risk of PAD-associated morbidity and mortality [31]. Based on data from the Global Burden of Diseases 2010 study, in 1990, the age-specific death rate per 100,000 population from PAD ranged from 0.05 in the 40–44 age group to 16.63 in people aged above 80 years worldwide. In 2010, estimates for the same age groups were 0.07 and 28.71, reflecting an increase in death rates related to PAD. PAD-related mortality increased considerably with age. Comparing Eastern and Western Europe, death rates attributed to PAD were found to increase between 1990 and 2010 from 1.37 to 4.58 per 100,000 population among women in Western Europe, and from 0.08 to 0.35 in Eastern Europe. Among men, changes in death rates

attributable to PAD ranged from 1.37 to 2.00 in 1990 and 2010 in Western Europe and from 0.04 to 0.09 per 100,000 population for the same years in Eastern Europe [24]. Taking a closer look at European countries, according to the most recent data from the GBD study, age-standardised mortality due to PAD per 100,000 population was considerably low in Greece in 1990 (0.35 in males, 0.34 in females), Iceland (0.48 in males, 0.6 in females) and Finland (1.35 in males, 0.97 in females) compared with the European average of 2.68 in males and 1.42 in females, with very small changes by the year 2019: Greece (0.36 in both sexes), Iceland (0.5 in both sexes) and Finland (1.6 in males, 1.12 in females) compared to the European average for 2019 of 2.98 deaths per 100,000 attributable to PAD. In contrast, Hungary had the highest death rates due to PAD in both sexes (7.05 in males, 3.07 in females) in 1990, and sadly maintained the highest rates in 2019 (7.79 in males, 3.06 in females), followed by Ukraine (5.02 in males), Russia (4.83 in males), and in the case of females, the Netherlands (2.35), Austria (2.17) and Russia (2.13) in 1990. The lowest mortality rates in 1990, in males, were found in Greece (0.35), Iceland (0.48) and Finland (1.35); in females, in Greece (0.34), Iceland (0.6) and Romania (0.82). In 2019, the same countries maintained top positions, following Hungary, in terms of PAD-related mortality with considerable increase among males in Ukraine (5.97) and Russia (6.28) and fewer changes among females in the Netherlands (2.58), Austria (2.58) and Russia (2.47). Countries with the lowest mortality rates experienced increase at significantly smaller scales: mortality rates in Greece rose to 0.36, in Iceland to 0.5, and in Finland to 1.6 among men. Among women, Iceland witnessed a slight decrease down to 0.5 deaths per 100,000. Greece had a slight increase up to 0.36 and Romania reported 1.02 deaths **(Figures 2 and 3)**.

According to GBD data, in 2019, PAD accounted for 0.13% of total deaths (0.074–0.23%) globally, including both sexes and all ages with a mean annual percentage change of 1.82%, between 1990–2019 [45].

Figure 2. Age-standardised mortality due to PAD per 100,000 population in some European countries and Europe, among females, between 1990-2019.
(graph by authors, source: https://vizhub.healthdata.org).

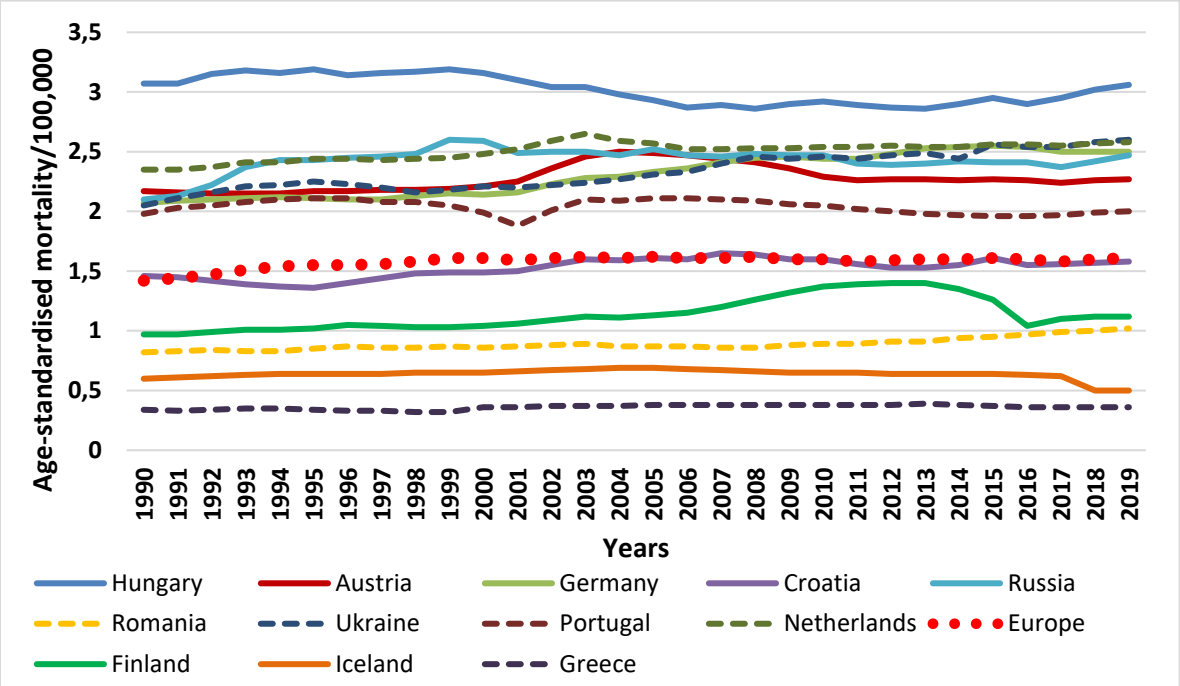
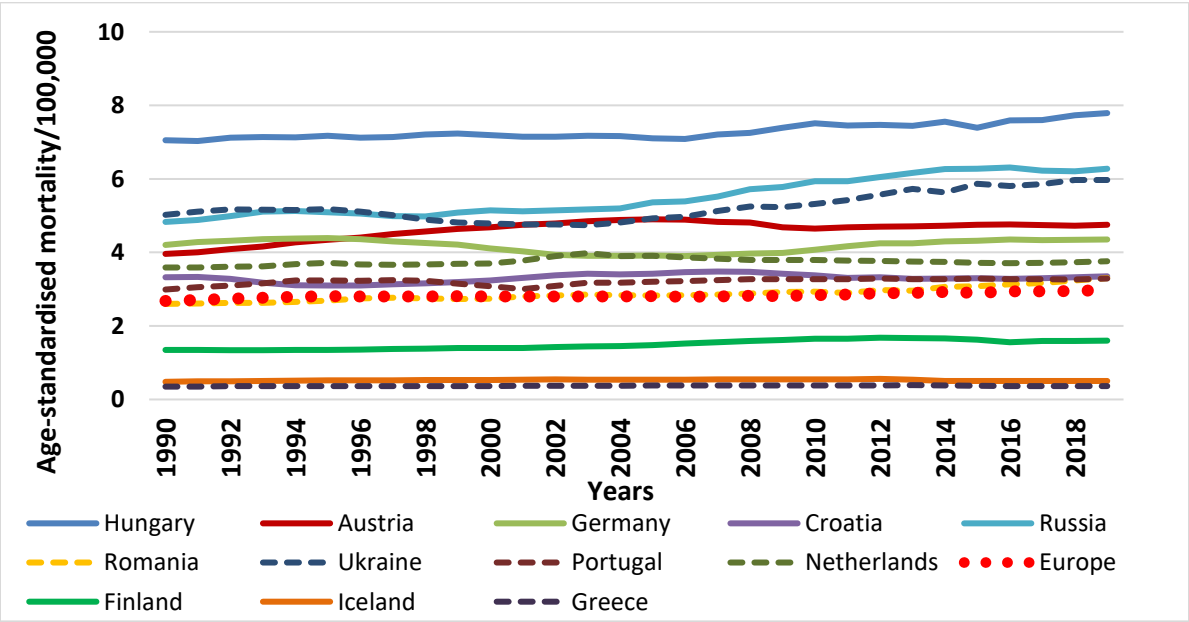


Figure 3. Age-standardised mortality due to PAD per 100,000 population in some European countries and Europe, among males, between 1990-2019.
(graph by authors, source: https://vizhub.healthdata.org).



According to the same source, in 2019, PAD accounted for 0.78% (0.32–1.6%) of total deaths in Hungary. Among males, PAD accounted for 0.92% of total deaths (0.31–2.27%) with a mean annual percentage change of 1.81%, between 1990 and 2019. Among females, PAD was responsible for 0.65% of the total death rate (0.24–1.65%); the mean annual percentage change was 2.04% during the same time period. Mean annual change in PAD mortality between 1990 and 2019 was 1.9% for both sexes in all ages. In 2019, 10.45 deaths per 100,000 (4.02–22.35) occurred due to PAD in Hungary [45].

4. PAD Risk Factors, Comorbidities and Major Adverse Limb Events

Atherosclerosis is a systemic disease and around 60% of PAD patients are expected to have ischaemic heart disease and one third cerebrovascular disease [52]. Approximately 5 years after diagnosis, 10-15% of patients with IC are highly likely to die of CVD. Therefore, it is of pivotal importance to identify and target risk factors that are in the background of PAD, heart disease and stroke [53]. A systematic review including 20,278 patients from 17 studies concluded that around half of all PAD is attributable to smoking. Despite quitting, past smokers have a persistently increased risk compared with never smokers [54]. Diabetes is the other crucial modifiable risk factor. TASC II. guidelines stated that diabetes puts patients at equal risk of developing PAD as smoking [52]. Studies mentioned above also found that patients with ABI < 0.90 were more likely to be smokers, to have hypertension and to suffer from symptomatic or asymptomatic CVD. Marital and socioeconomic factors, especially in men, with seperation/divorce, unemployment, and lower educational achievement, have been associated with a lower ABI [49, 50]. Besides age and female sex, several smaller studies have also highlighted smoking and diabetes as important risk factors for the development of PAD.

Although authors found lower PAD prevalence in an urban population in South India compared to studies in Europe and the USA in 2000, PAD prevalence was 6.3% among diabetics [55]. Another study by Krishan et al. revealed high age-adjusted prevalence of PAD (26.7%) in Kerala, India. Asymptomatic PAD was more prevalent among women (25.35% vs. 20.37%, p= 0.0485). Authors attributed the high prevalence of PAD to the high frequency of risk factors, especially smoking [56].

The impact of ethnic background on PAD prevalence has also been extensively studied. According to a recent study, Cuban Americans were significantly afflicted by PAD (9.1%) and had a three-fold higher prevalence (OR: 2.9, 95% CI: 1.9-4.4) compared to Mexican

Americans or other ethnic groups with Hispanic/Latino background. Authors suggested the high smoking rate as a possible confounding factor besides genetic predisposition [57].
A high prevalence (15.0%) of PAD was revealed among the elderly (>65 years) in the general population of two cities in Central Africa; PAD prevalence showed an association with hypertension, diabetes and increasing age [58].

5. PAD, Diabetes and Major Adverse Limb Events

Lower limb amputations are one of the most devastating consequences of PAD and diabetes [51]. Diabetic patients were shown to have a 5-fold higher amputation risk, worse PAD outcomes and higher mortality rates compared to non-diabetic patients with a similar history of smoking, ischaemic heart disease and hypercholesterolaemia in the United Kingdom. Even upon receiving up-to-date therapies, patients with PAD and diabetes are at higher risk of developing adverse limb events compared to those patients with PAD alone [59]. Outcomes of the COMPASS trial revealed that subsequent to the first major adverse limb event, the cumulative risk of repeated hospitalisation was 61.5%, for vascular amputations 20.5% and for death 8.3% among patients with LEAD. MALE was associated with significantly worse prognosis [38]. Race and socioeconomic status have been shown to independently affect the risk of a major amputation in PAD with black patients having a 37% higher risk than white patients. Black patients have been found to have more severe PAD status at presentation [60]. Studies have also shown that there has been no change with respect to racial disparities in vascular outcomes as black patients continue to experience higher major adverse limb events (HR 1.15 [1.06–1.25], $p < 0.001$), and amputation rates (HR 1.33 [1.18–1.51], $p < 0.001$), irrespective of the region in the USA [61, 62]. Caring for amputees poses a substantial economic burden for healthcare systems and results in a significant decrease in quality of life for the individual. Lower limb amputation rates as distal outcome indicators may shed light upon the effectiveness of various preventive and therapeutic approaches and thus may prove essential in evaluating vascular care [63].

6. Lack of PAD Awareness

Disease awareness is pivotal in designing and implementing targeted awareness campaigns. Despite the high prevalence and associated mortality risk of PAD, large

population-based studies have demonstrated suboptimal levels of knowledge of PAD in the Netherlands (20% aware), Canada (36% aware), the United States (26% aware) and Ireland (18% aware) in the general population and affected patient populations alike. Authors observed an unexpectedly low familiarity with PAD terminology, symptoms, and accompanying risk factors. Strikingly, familiarity with preventive and treatment options by lifestyle changes including cessation of smoking was also surprisingly low. Lower levels of education and lower socioeconomic status have been found to be associated with more significant gaps in public knowledge regarding risk factors, symptoms and consequences of PAD [14, 15, 16, 17].

7. PAD and Depression

Functional impairment and pain resulting from lower extremity arterial ischaemia may lead to significantly reduced quality of life, consequently, PAD patients may experience severe depressive symptoms. In a cross-sectional study comprising 300 individuals recruited from general practitioners' offices, Tóth-Vajna et al. examined the association between depressive symptomatology and peripheral artery disease. The study revealed a strong relationship between depression and PAD with 63% prevalence of depression among 'PAD-positive' patients and 59% in symptomatic patients without ABI abnormalities; prevalence was 20% in the noncompressible artery group compared to 8% prevalence among those without any signs of PAD, the group the authors called 'clear PAD negative' [6]. A study conducted in the USA also highlighted the increased prevalence of depressive symptoms among people suffering from PAD, mainly, resulting from impaired lower extremity functioning [7].

8. Disease Burden: Direct and Indirect Costs of PAD

A comprehensive assessment of global and regional burden of death and disability from PAD revealed that HICs are more affected by PAD than LMICs. Authors used the Disability Adjusted Life Years (DALY) to measure population burden and found the largest DALY rates, per 100,000 population, in the years 1990 and 2010, in the same high-income regions of Australasia, Western Europe, and North America. Regarding Europe, Central European countries were found to have DALY rates around half that of high-income Western European countries and twice as high as low-income Eastern European

countries [24]. A recently published systematic analysis for the GBD Study 2016 investigated global, regional and national incidence, prevalence and years lived with disability (YLDs) for 328 diseases and injuries for 195 countries and territories from 1990 to 2016. PAD accounted for 520,000 (244,000–941,000) YLDs in 2016. Percentage change in counts between 2006 and 2016 was 25.5% (23.8–27.3); percentage change in age-standardised rates between 2006 and 2016 was −5.9 (−6.8 to −5.0). For the year 2016, authors revealed a less than two-fold difference in age-standardised YLD rates for all causes between China, the country with the lowest rate (9201 YLDs per 100,000; 6862–11,943 per 100,000) and Yemen, the country with the highest rate (14,774 YLDs per 100,000; 11,018–19,228 per 100,000). The relative contribution of YLDs to the total burden of disease in DALYs increased from 21.7% (17.2–26.6) in 1990 to 33.5% (27.4–39.7) in 2016, reflecting the fact that the aging of populations is a global phenomenon with the inevitable consequence of people have to live more years with diseases than before and the growing number of people needing chronic care [1]. Regarding Years of Life Lost (YLL), recent data from the Global Burden of Disease Study revealed alarmingly high rates of age-standardised YLL in Hungary in both sexes (131.0 in males, 78.5 in women per 100,000 population) in Europe, followed by Russia (108.7 in males, 32.4 in females per 100,000 population) and Ukraine (101.7 in males, 33.6 in females per 100,000 population) in 2019. Countries with the lowest YLL, per 100,000 population, in Europe in 2019 included Greece (5.1 in males, 4.1 in females), France (11.8 in males, 5.6 in females), Iceland (6.6 in both males and females) and Finland (20.6 in males, 12.0 in females) **(Figures 4-5.)**.

Figure 4. Age-standardised YLL per 100,000 in some European countries among men, in 2019

(graph by authors, source: https://vizhub.healthdata.org).

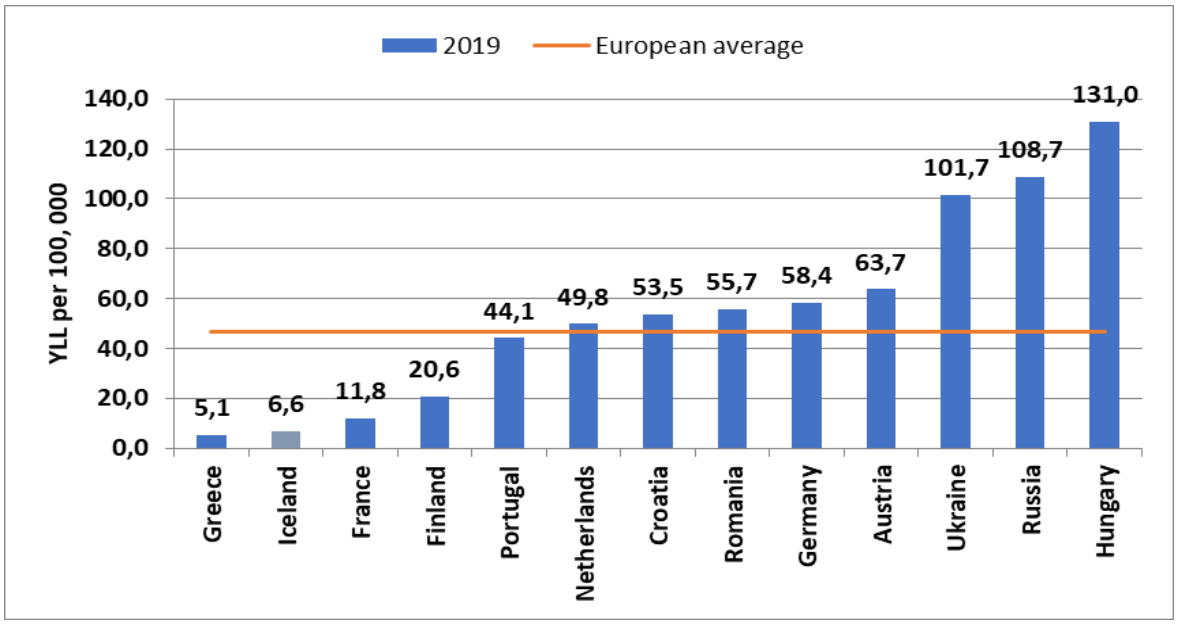
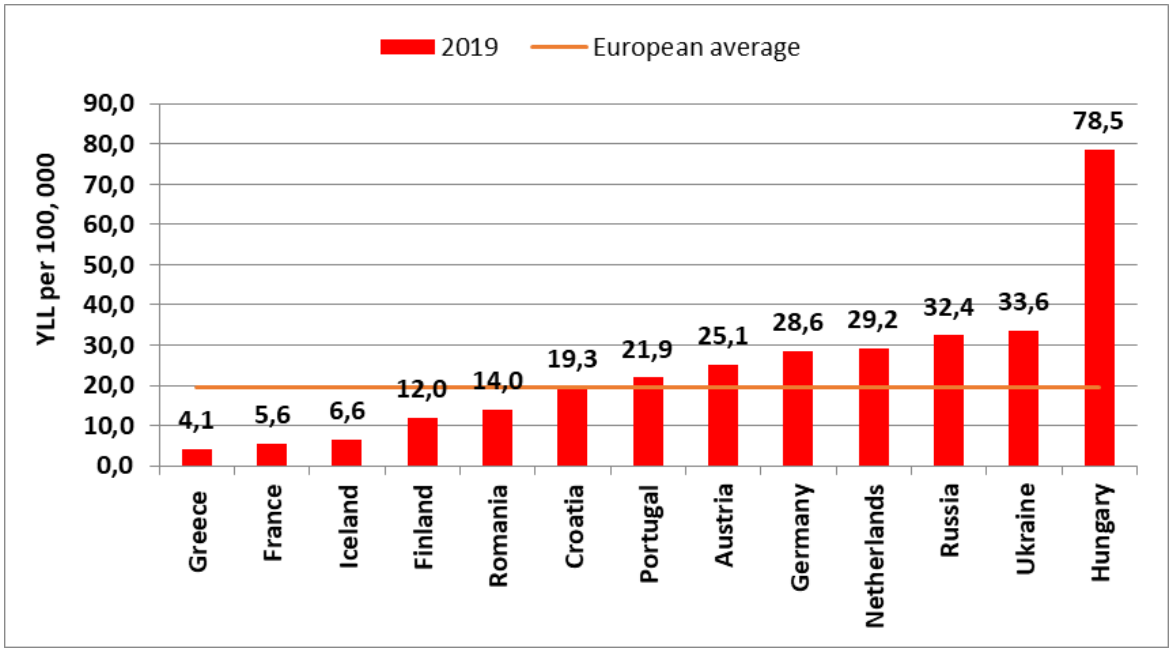


Figure 5. Age-standardised YLL per 100,000 in some European countries among women, in 2019

(graph by author, source: https://vizhub.healthdata.org).



9. Hungary

The present paper intends to devote special attention to Hungary, as our country has continued to have significantly high amputation rates, amputation-related mortality and PAD-related mortality. In Hungary, cardiovascular diseases account for more than half of total mortality [64]. The largest national epidemiological study with the inclusion of 21,892 men and women with hypertension (mean age 61.45 years) revealed very high prevalence of asymptomatic PAD (14.4%) in Hungary. Patients with ABI 0.91–0.99 accounted for 15.6% and patients with ABI > 1.3 accounted for 9.4% of the study population [65]. A retrospective cohort study was conducted within the framework of the HUNgarian VASCular DATA (HUNVASCDATA) project, based on healthcare administrative data for the whole Hungarian population covering the years 2004–2012. Authors analysed changes in PAD-related major amputation rates and revealed that there was no significant change in this respect in Hungary. Compared to the European Standard Population (ESP), the incidence of lower limb major amputations was drastically high at 42.3/100,000 in the total population, with 50.4% of amputees being diabetic. During the study period of 9 years, 76,798 lower limb amputations were performed, out of which 71.5% were primary amputations [9]. Started in 1997, VASCUNET is a collaboration of registries for vascular surgery in Europe, Australia, New Zealand, and Brazil with the aim to create a common international dataset on vascular surgery, to promote the understanding of vascular disease and share knowledge in the field of vascular surgery [66]. According to the 2018 VASCUNET report based on data reported by 12 countries including 259 million inhabitants, covering the period 2010–2014, Hungary had an alarmingly high incidence rate of major (above the ankle) amputations. In the ≥65 age group, Hungary had the highest rate of major amputations compared to the general population. The incidence of major amputations was 3.5 times higher among the elderly compared with all age groups. With an incidence of 41.4/100,000, Hungary performed at the highest end of the spectrum with the highest amputation-related mortality rate of 20.3%. Regarding smoking as a predisposing factor, the proportion of active smokers was also the highest in Hungary with 25.8%. Authors found an association between higher amputation rates, lower socioeconomic status and healthcare expenditures [10]. A more recent study investigating lower limb amputation and revascularisation procedures highlighted a 10-year delay regarding the start of a declining tendency in amputation rates. The study by Kolossváry et al. analysed inpatient administrative data claims for the entire beneficiary population of

Hungary over a period of 14 years (2004–2017) and included both major and minor amputations. Authors observed a slight decline in major amputations (15%) from 2013 and a 79% growth in the number of endovascular procedures performed (based on crude rates), a pattern observable in developed countries. As a consequence of 'endovascular first' strategies being adopted and becoming increasingly widespread, other Western European countries witnessed this trend a decade earlier. In Hungary, the crossing of the two trend curves occurred in 2015. Despite the promising trend, authors emphasised the fact that compared to developing countries, endovascular procedures accounted for a significantly lower segment of the volume of vascular procedures during the period under investigation [63]. Early recognition of LEAD is of pivotal importance as patients with vascular diseases have 2–4-times higher risk of developing cardio- and cerebrovascular events in the future [5, 25]. The majority of PAD patients are asymptomatic, and thus may remain undiscovered and untreated without targeted screening [5, 33]. A large epidemiological study with the inclusion of 816 individuals investigated the prevalence of PAD among patients screened in primary healthcare settings in Hungary with the aim to improve the efficacy of screening, with a special focus on patients with ABI negative symptomatic status or non-compressible arteries. Among the study population, 52% (n = 425) of the patients were clear PAD negative, 23% (n = 185) were clear PAD positive, 13% (n = 109) had normal ABI but were experiencing symptoms of walking impairment, and 12% (n = 97) belonged to the non-compressible artery group (ABI> 1.4). The risk factors profile of the ABI negative symptomatic subgroup was very similar to those of the other subgroups with hypertension (81%), diabetes (35%), active smoking (28%), myocardial infarction (23%) and stroke (13%) in the past medical history. In line with findings of the PAOD (Peripheral Artery Occlusive Disease) study [30], the above Hungarian study calls special attention to the high prevalence of PAD in the general population and the significant role of multiple risk factors, emphasizing the important role of general practitioners in the early recognition and treatment of PAD and stresses the importance of further testing in ABI negative patients [67]. Another study, also in a primary care setting in Northern Hungary, between 2015–2017, involving 680 patients, further emphasised the fact that among patients comprising the so-called 'murky zone', i.e., ABI negative symptomatic patients (14%), and those with non-compressible arteries (12%), ABI screening may often not suffice in detecting patients suffering from PAD [68]. Apart from highlighting the high national prevalence of PAD and the significant presence of risk factors, recent studies conducted in Hungary underline the importance of targeted screening for the disease, and

the important role of general practitioners in preventive and therapeutic efforts especially in areas of the country with lower socio-economic conditions and suboptimal access to healthcare [67, 68].

10. Conclusions

Considering an increasing life expectancy, and the global epidemiological transition towards an older age distribution, people are expected to live longer years with chronic conditions that significantly impact quality of life [2]. Chronic ill health causes a significant burden for patients, not only in terms of acute or chronic pain but also as a result of limitations that may alter patients' ability to work, to engage in social activities, or to be actively involved in family life. The global burden of PAD has increased over the past decades with developing regions of the world having witnessed a more striking increase in PAD-attributable disease burden [1, 24]. Administrative data may not be sensitive enough for identifying all forms of PAD in communities [35]. Consequently, early detection of PAD, especially among asymptomatic patients or those with atypical symptoms, is of pivotal importance as PAD has remained underdiagnosed and undertreated [32, 35, 67, 68]. Regardless of advances in treatment modalities, outcomes especially among patients with CLI have remained unfavourable in LMICs and HICs as well [38]. The number of PAD patients has been markedly rising, causing an increasing disease burden to healthcare systems globally [24, 38]. PAD is associated with significant morbidity and mortality from cardio- and cerebrovascular diseases and patients have an equal risk of suffering a future stroke or MI as patients with coronary artery disease [31]. The management of PAD patients accounted for considerably high percentages of in-hospital and healthcare costs [32]. PAD is associated with considerable physical and psychosocial disease burden, primarily, due to impaired functional status and deterioration in quality of life [11, 12, 39]. Despite the spread of up-to-date limb salvage interventions, the number of PAD-related major and minor amputations has not decreased at optimal rates, especially in Eastern European countries [10, 63]. A comprehensive knowledge of the disease burden attributable to PAD, the evaluation of the improvement in quality of life achieved via the latest pharmacotherapeutic and surgical interventions, together with addressing the issues relating to risk factor reduction, particularly the promotion of smoking cessation and the management of diabetes mellitus and hypertension are, therefore, equally important in both developed and developing regions of the world [69].

The management of CV risk factors includes smoking cessation, healthy diet, physical activity, and controlled exercise training. Pharmacological therapy is aimed at the management of hypertension, diabetes, lipid control (statin, ezetimibe) and adequate antiplatelet therapy [5]. Resource-limited countries will also need to prioritise early detection and treatment of PAD as this disease is expected to remain a major and crucial public health challenge in the foreseeable future.

4. TRANSLATION CHALLENGES DURING THE LINGUISTIC VALIDATION OF PADQOL (PERIPHERAL ARTERY DISEASE QUALITY OF LIFE) QUESTIONNAIRE INTO HUNGARIAN[2]

As past decades have seen a considerable increase in the number of multinational and multicultural research projects, the need for the translation and cultural adaptation of health status measures to other countries and cultures has also grown rapidly. The linguistic validation of self-administered health-related quality of life (HRQoL) questionnaires requires a unique method to ensure both linguistic and cultural equivalence between the original, source (SL) and target language (TL) versions. Peripheral artery disease (PAD) is a global burden affecting >200 million people worldwide and as a progressive atherosclerotic disease, it is associated with increased morbidity and mortality. Hungary has seen an alarmingly high level of major amputations related to PAD; therefore, our aim is to provide a further validated tool that can assess the subjective disease burden patients with PAD experience. PADQoL is a validated questionnaire (Treat-Jacobson et al., 2012), designed to assess disease-specific physical, psychosocial and emotional effects of PAD. Our aim is to develop a valid Hungarian version of the original PADQoL, through the translation, cultural adaptation and content validation of the original instrument. The paper outlines main features of generic and disease-specific HRQoL measures and provides insight into the main steps of the linguistic validation process of PADQoL as conducted according to an international guideline: two initial translations, synthesis of the two translations, backward translations and expert committee assessment to compare translations and create the pre-final version. Additionally, challenges posed by several of the items in terms of lexical and grammatical transfer operations, idiomatic and cultural equivalence are discussed.

[2]*The chapter is based on the article:*
***Horváth L**, Elmer D, Németh N, Boncz I, Endrei D. Translation challenges during the linguistic validation of PADQoL (Peripheral Artery Disease Quality of Life) questionnaire into Hungarian. In: Darija, Omrcen; Vesna, Cigan (Eds.) IV. International Conference From Theory to Practice in Language For Specific Purposes. Conference Proceedings. Zagreb. 2019; 101 pp.60-70.*

Introduction

The WHO defines Quality of Life as the ‘individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment [70].

In clinical practice, the assessment and evaluation of quality of life is primarily aimed at measuring the impact of a particular medical condition on the individual patient's well-being, in terms of physical and mental health, including activity levels, social relationships and emotional health and it also focuses on evaluating the effect of treatment modalities upon all these aspects of life. Chronic ill health may cause a significant burden for patients, not only in terms of acute or chronic pain but also as a result of limitations that may alter patients' ability to work, to engage in social activities, maintain friendships or to be actively involved in family life.

Consequently, chronic diseases do not only affect physical health but have a significant negative impact on several aspects of life causing a considerable decrease in the feeling of “competence“, resulting in a marked decline in subjective quality of life that may further deteriorate health status [71] .

Considering an increasing life expectancy, and the global epidemiological transition towards an older age distribution, people are expected to live more and more years with chronic conditions that significantly impact quality of life. In response to the above phenomenon, the assessment of health-related quality of life has gained more importance in clinical studies.

As the past decades have seen a considerable rise in the number of multinational and multicultural research projects, the use of HRQoL instruments in these studies and consequently, the need to translate and adapt these health status measures for use in other than the source language has also grown rapidly [21].

Herdman et al. highlighted that the increasingly international nature of drug trials has created a demand for translated instruments, primarily, to enable comparison or aggregation of results across different language groups [23]. In terms of health policy, there is a need for indicators that can be used in monitoring the health of populations and

for programme evaluation. Increasing attention is also being paid to cross-cultural comparisons of effective interventions and preferences for different states of health in order to facilitate the extrapolation of results from effectiveness and cost-effectiveness studies from one country to the other.

General and disease-specific quality of life instruments

Clinical studies measure and evaluate changes in HRQoL from various aspects and several questionnaires have been developed for this purpose [18, 19].

Generic quality of life instruments, e.g. SF-36 or EuroQoL-5D assess physical and social functioning, bodily pain, general mental health, vitality and general health perceptions. General quality of life questionnaires are designed to be applicable across a wide range of populations and interventions. However, these generic measures are considered to be less effective in detecting relatively small differences in terms of treatment efficacy which may, nevertheless, be crucial from a clinical perspective.

Disease-specific quality of life questionnaires, on the other hand, are developed and constructed to assess changes in quality of life in certain subpopulations, in patients suffering from a particular disease, or prior to and after particular therapeutic interventions. The use of both generic and disease-specific questionnaires is required in quality of life research [72] [73]. Although generic and disease-specific questionnaires performed equally well, de Vries et al. found that the disease-specific questionnaire they used, (VascuQoL), was superior in discriminating between large versus small change in disease severity after follow-up [20].

Peripheral artery disease (PAD)

PAD, also called lower extremity artery disease (LEAD), is a progressive atherosclerotic disease of the lower extremities, associated with concomitant coronary and cerebrovascular disease and an increased risk of mortality and morbidity due to cardio- and cerebrovascular disease [13, 74]. The most common symptom of PAD is claudication, which is characterised by pain, cramping or aching in the calves, thighs or buttocks, initiated by walking, and subsiding with rest [22]. Further symptoms may also include atypical pain on

exertion and ischaemic pain at rest. The final stages may result in tissue loss and amputation. PAD may remain asymptomatic for a while, but symptomatic PAD is associated with severe limitations in physical function, especially walking and a wide range of daily activities. 70-80% of the death of PAD patients is caused by cardiovascular disease. PAD is not deadly in itself but is a significant predictor of the extent of systemic vascular disease [64]. A recent systematic review reported that more than 200 million people are affected by PAD worldwide with substantial increase in prevalence over time. Consequently, the global burden of PAD is immense [8]. According to the 2017 European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of peripheral arterial diseases, PAD and diabetes are the major causes of lower limb amputations throughout the world [5]. In Hungary, cardiovascular diseases account for more than half of total mortaliy. PAD affects approximately 400,000 people; its prevalence may reach 20% among patients aged ≥ 50 years [64]. A questionnaire survey found that disease progression in PAD is associated with significant reduction in quality of life [27]. A recent, nationwide study revealed the sad fact that during the 9 years analysed (2004 - 2012) there were no significant changes in PAD-associated lower limb major amputation rates in Hungary [9]. Another study comparing amputation rates among patients with PAD, found that Hungary had an alarmingly high incidence of major amputations, performing at the higher end of the spectrum with an incidence of 41.4/100.000 [10]. Furthermore, Hungary was found to have the highest reported amputation-related mortality rate of 20.3%.

PADQOL

PADQOL is a disease-specific questionnaire developed by Treat-Jacobson and colleagues with the aim to provide a further validated tool for the assessment and evaluation of the impact of PAD on HRQoL from the aspect of subjective burden of disease [22]. The 38-item questionnaire investigates five factors: social relationships and interactions (9 items), self-concept and feelings (7 items), symptoms and limitations in physical functioning (8 items), fear and uncertainty (4 items), positive adaptation (7 items) and contains three individual items on job, sexual function and intimate relationships. Response options range from “strongly agree” to “strongly disagree” on a Likert-type scale. The completion of the original questionnaire took patients 5-10 minutes. According to Treat-Jacobson et al. their

aim was to develop a questionnaire that, besides limitations in physical functioning, focuses more on subjective, perceived social and emotional burden of PAD and its effects on well-being and quality of life, as PAD can even "compromise a patient's sense of self" [22]. PADQOL is different from other existing PAD-related health-related quality of life instruments in that it is able to assess relative differences for the individual patient and may thus provide a useful guidance to clinicians to tailor treatment strategies and to help identify patients who would benefit from additional therapies including psychotherapy or social support [22].

Methods

The cross-cultural adaptation of a health-status self-administered questionnaire for use in a new country, culture and/or language necessitates the use of a unique method, to reach equivalence between the original source (SL) and target language (TL) versions of the questionnaire. It has been recognized that if measures are to be used across cultures, the items must be adapted culturally to maintain the content validity of the instrument at a conceptual level across the different cultures. The term "cross-cultural adaptation" is used to encompass a process that looks at both language (translation) and cultural adaptation issues in the process of preparing a questionnaire for use in another setting [21]. The aim, therefore, is to produce a translation that is both culturally and linguistically equivalent to the original source language version. Translation difficulties may arise from: cultural differences between the SL and TL, ambiguous original items including confusing words, stylistically inappropriate item writing, technical terminology and grammatical inconsistencies may also pose problems for translators [75]. In a review of definitions of equivalence in health-related quality of life literature, Herdman et al. distinguish 19 different types of equivalence and claim that for a translated instrument to be functionally equivalent, it is to produce the same responses from the patient the original would [23]. When discussing the translated Hungarian versions of the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, the consensus team had to solve a problem arising from a cultural/experiential difference, as described by Varjú et al. [76] as follows: " as golf is hardly known in Hungary, the expert team decided to use both 'golf' and 'dusting the carpet' which is a well-known activity in the country and in the 19th item (frisbee is uncommon in Hungary) using both "playing frisbee" and 'throwing a beach-ball' were

accepted, to ensure cultural/experiential equivalence." During the translation process of PADQoL, none of the items caused problems in terms of finding culturally or experientially equivalent solutions.

PADQOL: the translation process

After consulting and comparing several linguistic validation guidelines, our team conducted the translation process according to the protocol by Beaton et al. as outlined in **Table 1** [21].

Table 1. The translation process of PADQOL

Step 1. Permission from first author	**Participants:** Prof. Treat-Jacobson gave the permission for the linguistic validation of PADQOL	**Aim:** To ensure authors' copyright and legal clarity.
Step 2. Forward translations T1, T2	Two certified translators (an informed translator: specialised in medical translation and an uninformed translator with a different background) native in TL, fluent in SL. The informed translator received information about the aim of the questionnaire, and concepts being examined.	Working from the original the two forward translators translated the questionnaire, introduction, items, and response options into TL. The uninformed translator was expected to produce a translation that better reflected the language used by the general population.
Step 3. Consensus (T3) of forward translations T1 & T2	A third certified translator (first author of this article) reviewed T1 and T2 with the two forward translators.	The three translators reviewed translations, discussed inconsistencies and agreed upon a consensus version.
Step 4. Back translation	Working from T3, totally blind to the original, two back translators, with non-medical background, native in SL, fluent in TL, created two back translations.	To highlight gross inconsistencies or conceptual errors.
Step 5. Consensus	Forward translators, back	To consolidate all versions

meeting	translators, medical professionals, (here: internists with a specialisation in angiology), a methodologist and an applied linguist discussed all translations.	of the questionnaire and reach a consensus on discrepancies and create the **pre-final version.**
Step 6. Piloting of pre-final Hungarian version	Pilot patient population: (n=30), native in TL, adequately represent target population socio-demographically and clinically: age, sex, education, diagnosis, previous interventions including revascularisation and comorbidities.	Thirty patients are asked to complete the questionnaire during cognitive interview sessions, with the aim to identify items that are difficult to understand, to test alternative translations or to highlight items that may be inappropriate at a conceptual level.

During the translation of PADQOL into Hungarian, as we were translating from a language having an analytical construction to a language with a synthetic construction, the following lexical and grammatical transfer operations were the most common as described by Klaudy [77]:

- Narrowing of meaning (specification)
- Broadening of meaning (generalisation)
- Grammatical omission (prepositions, modal words)
- Grammatical transposition (word order)
- Grammatical division (finite form clauses)
- Grammatical replacements (simpler verb forms)

Results and discussion

Both forward translators had a Master's degree in English Studies, were certified translators and interpreters, one translator was specialised in medical and health-sciences translation and interpreting and the other translator had a post-graduate certificate in economics and social sciences translation and interpreting. As the original English version of the PADQoL questionnaire does not include any medical terminology, only the acronym PAD for peripheral artery disease, the two forward translations did not reveal significant

differences in terms of a more patient-friendly versus a more medically accurate translation.

Twenty-six out of the thirty-eight items and the introduction to the PADQoL questionnaire contain the acronym PAD, e.g. “Item 3.: I cannot do many of the things I enjoy because of my PAD”. As PAD is not a well-known acronym in Hungarian, not even among medical professionals specialised in other areas of medicine than internal medicine, angiology or cardiology, the consensus team decided to provide the full translation/definition in the introduction, but to use the term “érszűkület” (in English: vascular narrowing) instead of the acronym PAD in all subsequent items as this is the term Hungarian patients suffering from peripheral artery disease use when they refer to this disease and consequently, this is the term they would most readily understand. Furthermore, as Hungarian people would typically add the possessive first person suffix –m (meaning: “my”) when talking about their diseases and conditions instead of PAD, the Hungarian items have “érszűkülete**m**”, meaning: “my vascular narrowing”. Therefore, the consensus Hungarian version of the above item was: “Az érszűkületem miatt, sok olyan dolgot nem tudok csinálni ami örömet okoz.”

Item 23. of the PADQoL measure posed a translation challenge as the Hungarian word for function, “működés” is not used in this context at all and the solution offered by the other translator: “teljesítmény” meaning “performance” would not be adequate either, as PAD affects just as many female as male patients, and female patients could not relate to a question asking about their sexual performance with respect to PAD. As demonstrated in **Table 2.**, at the forward translation consensus meeting the translators agreed to render “sexual function” as “szexuális élet=sexual life”, a solution that was supported by angiologist physicians and linguist colleagues as well at the final consensus session.

Table 2. Item 23. of PADQoL

Original item 23.	**“I am very satisfied with my sexual function.”**
T 1.	Kifejezetten elégedett vagyok a szexuális **működés**emmel.
T 2.	Nagyon meg vagyok elégedve a szexuális **teljesítmény**emmel.
T 3.	Nagyon elégedett vagyok a **szexuális élet**emmel.
Consensus version	**Nagyon elégedett vagyok a szexuális életemmel.**

Table 3. below shows, that PADQoL item 26. has the expression ‘not normal’ in quotation marks, indicating that it should not be interpreted literally. Although both forward translators offered a correct literal translation in Hungarian, retaining the quotation marks, at the forward translation consensus meeting the translators agreed to find a Hungarian expression that would most precisely give back the underlying meaning of the original, as in Hungarian, the connotative meaning of “not (being) normal=nem vagyok normális” is either that the person suffers from a mental disorder or that they do not conform to accepted societal norms. The solution, the expression “nem érzem teljes értékűnek magam”, in English: “I do not feel complete” was accepted by the consensus team as we were afraid patients would leave this item unanswered.

Table 3. Item 26. of PADQoL

Original item 26.	**“My PAD makes me feel ‘not normal’.”**
T 1.	A betegségem miatt nem érzem magam „normálisnak”.
T 2.	A PAD miatt gyakran az az érzésem támad, hogy nem vagyok „normális”.
T 3.	A betegségem (PAD) miatt már nem érzem teljes értékűnek magam.
Consensus version	**Az érszűkületem miatt nem érzem teljes értékűnek magam.**

The final consensus translation of Item 32., as shown in **Table 4.** below, intends to demonstrate our attempt to simplify sentence structures as much as possible and to offer translation solutions that would be easily understandable for elderly Hungarian patients besides retaining the concept the original item was intended to measure. Although T2

forward translation, (in English: “Due to my disease, I often feel that I have lost a part of my personality”) was very close to the original, the consensus team decided to use the expression “már nem vagyok a régi” (in English: “I’m no longer my old self”) which is commonly used by Hungarian patients when they complain about their general state of health.

Table 4. Item 32. Of PADQoL

Original item 32.	**“My PAD makes me feel that I’ve lost a part of who I am.”**
T 1.	A betegségem miatt már nem érzem magam annak, aki régen voltam.
T 2.	A betegségem miatt gyakran az az érzésem, hogy elvesztettem a személyiségem egy részét.
T 3.	A betegségem (PAD) miatt már nem érzem magam annak, aki régen voltam.
Consensus version	**Úgy érzem, hogy az érszűkületem miatt már nem vagyok a régi.**

Further items of PADQoL proved unproblematic as they were semantically, syntactically and conceptually easy to render into Hungarian.

Conclusion

The forward translation of PADQoL items caused no difficulties for the translators. Items were easy to render into Hungarian. The content comparison of the back translation with the original questionnaire showed that all items were conceptually and linguistically equivalent. Relevant issues with regard to more challenging items were resolved during the consensus meeting. Using a systematic and rigorous methodology, we created the pre-final version of PADQoL for use in Hungary that can undergo pilot-testing, the final stage of the cross-cultural adaptation process.

5. ADAPTATION OF THE PERIPHERAL ARTERY DISEASE QUALITY OF LIFE QUESTIONNAIRE INTO HUNGARIAN[3]

Peripheral artery disease is one of the greatest global public health concerns affecting more than 200 million people worldwide. The Peripheral Artery Disease Quality of Life questionnaire was developed to assess the subjective disease burden of peripheral artery disease by focusing on psychosocial and emotional effects besides physical symptoms and functional limitations. Our aim was to develop the valid Hungarian version of the original PADQOL via the standard linguistic validation and cross-cultural adaptation procedure.

The linguistic validation was conducted according to an international protocol: two independent forward translations, a synthesis of the translations, back translations and consensus team review. The pilot-testing of the 'pre-final' Hungarian version was conducted via cognitive interviews with 30 in- and outpatients attending the Department of Angiology. Factor analysis was performed, Cronbach-α values were calculated to establish the reliability of subscales and to determine the internal consistency of items. IBM SPSS 23.0 was used. The linguistic validation of PADQOL into Hungarian posed no difficulties in terms of semantic, experiential and idiomatic equivalence. One item was found difficult to interpret during cognitive interviewing. The 'pre-final' version of the questionnaire was easy to understand and complete. Cronbach-α values of factors ranged between 0.624-0.887. The lowest value was that of factor 4: Fear and Uncertainty (mean score:14.07).

The linguistic validation of PADQOL into Hungarian was successful, the final Hungarian version is a tool that should reveal valuable insights with regard to subjective disease burden of patients living with peripheral artery disease subsequent to psychometric and clinicometric validation on a larger patient population.

[3] *The chapter is based on the article:*
***Horváth L**, Boncz I, Kívés Zs, Németh N, Biró K, Fendrik K; Koltai K, Késmárky, G, Endrei D. A perifériás verőérbetegek életminőségét vizsgáló angol nyelvű kérdőív magyar adaptálása. Orv Hetil. 2020; 161(51): 2153–2161.*

Introduction

Peripheral arterial disease (PAD) or lower extremity arterial disease (LEAD) is a progressive, atherosclerotic disease affecting the lower extremities and is a diffuse, degenerative process. Insufficient blood supply and oxygenation, due to atherosclerosis, results in pain on exertion and at rest (intermittent claudication, ischaemic claudication) or, in severe cases, critical limb ischaemia [73]. PAD often remains asymptomatic for a long time and is often only detected when walking becomes restricted due to deteriorating blood supply or when a non-healing wound or ulcer develops on the legs. The pain caused by an arterial ulcer can be further complicated by local infection or inflammation. This can lead to severe discomfort, limited ability to carry out everyday tasks, a significant reduction in quality of life and, in severe cases, amputation [28, 78, 79].

PAD is a significant predictor of the stage of systemic vascular disease. A systematic review published in 2013 revealed that PAD was the third leading cause of atherosclerotic cardiovascular mortality after coronary heart disease and stroke. According to this study, the number of patients with PAD worldwide, in 2010, was estimated at 202 million, an increase of 28.7% over the 10 years studied (2000-2010). The prevalence of PAD has been increasing representing a significant global burden not only for patients but also for society and health care systems [8]. According to the 2017 European Society of Cardiology (ESC) guideline, PAD and diabetes are the leading causes of lower limb amputation worldwide [5].

Cardiovascular diseases are responsible for more than half of all-cause mortality in Hungary. Peripheral arterial disease occurs mostly in the arteries of the lower limbs, vascular narrowing is a sign of atherosclerosis. The disease affects around 400,000 people in Hungary, with a significant increase in prevalence above age 50, reaching up to 20 % [64, 80, 81]. Patients suffering from peripheral artery disease have a significantly higher risk of cardio- and cerebrovascular mortality; this population has a double risk of a future heart infarction or stroke [13, 74]. Pécsvárady et al. showed that 70-80% of the mortality of PAD patients is due to a cardiovascular cause [64]. Comorbidities also play a crucial role, primarily, high blood pressure, dyslipidaemia and diabetes mellitus. Smoking is one of the main life-style related risks [4, 74, 82].

Recent years have seen an increase in studies investigating PAD-specific quality of life and the impact of disease progression on quality of life [83]. Several studies have highlighted

the disease burden associated with peripheral artery disease as well. It has been shown that Health Related Quality of Life (HRQOL) deteriorates gradually with advancing disease as categorised by Fontaine stages [27]. In Hungary, the majority of the studies investigating the association between PAD and quality of life have been conducted using a generic measure, the EuroQol (EQ-5D) quality of life questionnaire [27, 72]. Generic and disease-specific questionnaires are both needed in quality of life research [72, 84]. Several studies have shown that, in addition to general quality of life measures, disease-specific questionnaires are effective in assessing the subjective burden of disease, psychosocial and emotional impact of PAD [20, 22].

PADQOL (peripheral artery disease quality of life) is the first self-administered disease-specific questionnaire that was developed to assess not only the physical symptoms of peripheral vascular disease but also the psychosocial and emotional impact of the disease, highlighting those subjective, individual aspects underlying patients' quality of life assessments that can indicate the need for social or psychological support [22]. Quality of life research and patient reported outcomes have become more popular and have gained more attention in Hungary during past decades [85, 86, 87].

Our aim was to linguistically validate and cross-culturally adapt the original English-language PADQOL questionnaire and thereby, to provide a valid, reliable assessment tool for use in Hungary. By validating PADQOL into Hungarian we intended to provide a new HRQoL questionnaire which can be an effective, more precise tool in assessing quality of life and the subjective disease burden in the Hungarian patient population and could also be used for monitoring change subsequent to pharmacotherapy or surgical interventions, thereby enabling the comparison of quality of life gained with international data.

Materials and methods

PADQOL questionnaire

The original PADQOL questionnaire was developed by Treat-Jacobson and colleagues based on interviews with 38 symptomatic patients with intermittent claudication, resting ischaemic pain, tissue loss and amputation in the United States with the aim to create a tool which can also measure the subjective feelings and problems experienced by PAD patients. The 65 items of the questionnaire, created in the first phase, were narrowed down to 38 items as a result of a multi-step validation process involving 297 patients [22].

The authors' aim was to create easily comprehensible items PAD patients would feel relevant and could relate to. PAD can have a significant impact on quality of life including relationships with family and friends, and can also have a major impact on patients' subjective self-image. The PADQOL questionnaire, in addition to items on the physical limitations caused by pain at rest or when walking, includes statements assessing the subjective burden of PAD in daily life, the impact of the disease on quality of life and the patient's well-being.

The 38-item PADQOL questionnaire examines health-related quality of life in 5 factors: social relationships and interaction (9 items), self-concept and feelings (7 items), symptoms and limitations in physical functioning (8 items), fear and uncertainty (4 items), positive adaptation (7 items), and 3 individual items on work, sexual life and intimate relationships. Response options are scored on a 6-point Likert-type scale ranging from 1 (strongly agree) to 6 (strongly disagree). Two of the individual items (sexual function, intimate relationships) and the summed scores on Factor 5 are reverse coded. PADQOL is easy to complete, according to authors, its completion requires an approximate 9 minutes [22].

Linguistic validation

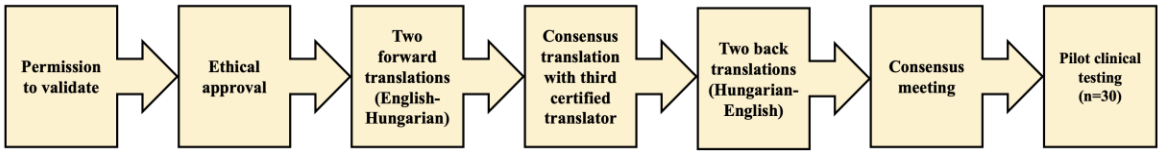
The linguistic validation process of the PADQOL questionnaire was based on an internationally used protocol [21, 88] *(Figure 1.).* As a first step, we requested and received a permission to validate and cross-culturally adapt the PADQOL questionnaire into Hungarian from the corresponding author, Prof. Diane Treat-Jacobson. We also received the final, formatted version of the questionnaire and the instructions regarding evaluation. Subsequently, two certified translators translated the questionnaire including

the introduction, items, and response options from English into Hungarian. The so called ‘informed’ translator was specialised in medical and health-sciences translation and interpreting and the other translator, the ‘uninformed’ translator, had a post-graduate certificate in economics and social sciences translation and interpreting. The ‘informed’ translator received information about the aim of the questionnaire and the concepts it was designed to investigate. As PADQoL is a self-administered health status measure, the two forward translators were recommended to focus more on maintaining conceptual, dynamic rather than formal equivalence. A third certified translator reviewed the two forward translations (T1&T2) with the two forward translators, discussed inconsistencies and agreed upon a consensus version (T3). As PADQOL does not contain medical terms besides the acronym PAD, there was no considerable difference between the two translations as could have been expected. The translators encountered no difficulties in terms of experiential or idiomatic equivalence. Working from the consensus version (T3), totally blind to the original, two back translators with non-medical background created two back translations. Back translators were native speakers of English, had been living in Hungary for more than 30 years, and were fluent in Hungarian. The back translations did not reveal gross inconsistencies or conceptual errors.

Back translations showed differences in 3 items where the translators used different expressions to maintain conceptual equivalence for example: in item 26. ’’My PAD makes me feel ’not normal’.’’ where instead of a mirror translation: „A PAD miatt nem érzem magam ‚normálisnak’.” the translators decided to use another expression: „Az érszűkületem miatt nem érzem teljes értékűnek magam.”, therefore, the back translation did not give back the original English expression.

The next step, according to the validation protocols was the consensus meeting. The consensus team consisting of the forward translators, the back translators, the third consensus translator, two internist-angiology specialist physicians, a linguist and an applied linguist reviewed and discussed all translations. The team reached a consensus on discrepancies and created the pre-final Hungarian version of PADQoL which then underwent pilot-testing through cognitive interview sessions involving 30 patients (**Figure 6.**).

Figure 6. The lingusitic validation process of PADQOL questionnaire



After receiving the approval of the Regional and Institutional Research Ethics Committee of the Clinical Center of the University of Pécs (PTE/1750/2019) we began the pilot-testing of the pre-final version of PADQOL at the Department of Angiology, 1st Department of Internal Medicine, Clinical Centre, University of Pécs, Hungary. In and outpatients suffering from symptomatic, Fontaine stage II-IV PAD above age 18 were included into our study. The 30 patients recruited for pilot-testing met future inclusion criteria. Mean age of the pilot population was 71.2 ± 10.4 years (15 females, 15 males). Prior to the cognitive interviews patients received information (in person and in writing) about the purpose of the study and signed an informed consent. Cognitive interviews were conducted using the so-called ’think aloud’and ’paraphrasing’techniques with the aim to assess the comprehensibility of the instructions, items and response options [89]. The experience gained from the cognitive interviews with 30 PAD patients showed that the Hungarian version of PADQOL was easy to understand and did not cause any difficulties. Item 6. ’Az érszűkületem miatt ért már valamilyen veszteség.’ was the only statement that caused difficulty for some patients to interpret as the word ’veszteség’ (loss) proved hard to interpret in the context of peripheral artery disease especially for patients having Fontaine stage II. PAD who did not yet suffer from severe pain and had no severe limitations in walking and were not significantly hindered in their everyday routine activities. A considerable proportion of the pilot population primarily associated the word ’veszteség/loss’ with finantial losses, especially those who were diagnosed with PAD after retirement and were no longer actively working. During cognitive interviews the word ’hátrány/disadvantage’ was offered as an alternative to patients which had also been considered during the translation process. As it seemed to help interpret the question, we decided to use both words in the Hungarian item to make sure both conceptual and lexical equivalence were maintained. The final Hungarian translation of item 6 was modified as follows: ’Az érszűkületem miatt ért már valamilyen hátrány vagy veszteség.’ We encountered no other contextual, conceptual or idiomatic issues in connection with items of the pre-final version of PADQOL. **(Figure 6**.)

Statistical methods

The main characteristics of the sample are presented by gender, with absolute and relative frequency scores (Table 5). The mean, standard deviation, minimum and maximum values of the summed and transformed scores for each factor were calculated (Table 6). In order to explore the factor structure of the instrument, factor analysis (main component analysis, Varimax rotation) was performed to reveal the internal structure of the PADQOL questionnaire (Table 7). The factor weights for each item are presented as their values are close to the values gained during the validation of the original measure indicating that the translation was successful. The reliability of the factors was assessed by calculating the Cronbach's alpha coefficient, which indicates the internal consistency of the items (Table 6)

Results

Demographic data, comorbidities and risk factors of the pilot population

The pilot population consisted of 15 female and 15 male patients. Mean age was 71.2±10. years, the youngest patient was 51, the oldest patient was 93 years old. The majority of patients were active smokers. More than half of the patients were diabetic (n=17), and all patients except for 2 suffered from high blood pressure, dyslipidaemia and cardiovascular disease.) 9 patients had had peripheral revascularisation previously. Regarding Fontaine stages, Fontaine II/b (n=12) and Fontaine IV (n=10) were the most common **(Table 5.)**.

Table 5. Demographics, comorbidities and risk factors of the pilot population

Variables	**Total (n=30) n (%)**	**Males (n=15) n (%)**	**Females (n=15) n (%)**
Smoking			
never	9 (30)	2 (13.3)	7 (46.7)
past	17 (56.7)	10 (66.7)	7 (46.7)
current	4 (13.3)	3 (20)	1 (6.7)
Diabetes			
yes	17 (56.7)	10 (66.7)	7 (46.7)
no	13 (43.3)	5 (33.3)	8 (53.3)
Hypertension			
yes	28 (93.3)	14 (93.3)	14 (93.3)
no	2 (6.7)	1 (6.7)	1 (6.7)
Dyslipidemia			
yes	28 (93.3)	14 (93.3)	14 (93.3)
no	2 (6.7)	1 (6.7)	1 (6.7)
CVD			
yes	28 (93.3)	14 (93.3)	14 (93.3)
no	2 (6.7)	1 (6.7)	1 (6.7)
Previous revascularisation			
yes	9 (30)	4 (26.7)	5 (33.3)
no	21 (70)	11 (73.3)	10 (66.7)
Fontaine stage			
II/a	5 (16.7)	2 (13.3)	3 (20.0)
II/b	12 (40.0)	7 (46.7)	5 (33.3)
III.	3 (10.0)	1 (6.7)	2 (13.3)
IV.	10 (33.3)	5 (33.3)	5 (33.3)

Internal reliability

The Cronbach's α values of the PADQOL dimensions/factors ranged from 0.642 to 0.887 in the pilot population which is similar to the reliability values of the original questionnaire developed by Treat-Jacobson et al. validated with 297 patients and reached an internal reliability value of 0.70 for all dimensions except 'Positive Adaptation'. Similar to the reliability scores published in the paper on the validation of the original questionnaire, the pilot-testing of PADQOL 'pre-final' Hungarian version found that Factor 5 'Positive Adaptation' showed the lowest reliability score (Cronbach's α=0.642) **(Table 6).**

Table 6. Cronbach's alpha values for PADQOL factors, comparison of the Hungarian instrument versus the original

Factors	**Cronbach alpha** (Hungarian version)	**Cronbach alpha** (Treat-Jacobson et al., 2012)
Factor 1. Social relationships and interactions	0.89	0.92
Factor 2. Self-concept and feelings	0.88	0.89
Factor 3. Symptoms and limitations in physical functioning	0.89	0.88
Factor 4. Fear and uncertainty	0.77	0.80
Factor 5. Positive adaptation	0.64	0.73

Factor analysis

Based on the score values of each factor, the '*Social Relationships and Interactions'* (Factor 1) and *Positive Adaptation* (Factor 5) factors showed the highest and thus the best scores (31.97 and 28.10, respectively). The factor *'Fear and Uncertainty'* (Factor 4) received the lowest score (14.07). Among the individual items, the '*Intimate Relationships'* item was reverse scored, so the high score here (5.4) indicated worse status **(Table 7).**

Table 7. Factor weights, items and reliability values measured on the pilot-testing of the 'pre-final' Hungarian version of PADQOL (n=30)

PADQOL factor	Mean (SD)	Possible range	minimum	maximum
Factor 1. summed score	31.97 (10.99)	9-54	15	54
Factor 1. transformed score	51.04 (24.42)	0-100%	13.3%	100%
Factor 2. summed score	20.90 (8.99)	7-42	7	37
Factor 2. transformed score	39.71 (25.68)	0-100%	0%	85.7%
Factor 3. summed score	21.13 (10.04)	8-48	9	48
Factor 3. transformed score	32.83 (25.09)	0-100%	2.5%	100%
Factor 4. summed score	14.07 (4.86)	4-24	6	24
Factor 4. transformed score	50.33 (24.32)	0-100%	10%	100%
Factor 5. summed score	28.10 (6.22)	7-42	13	41
Factor 5. transformed score	60.29 (17.78)	0-100%	17.1%	97.1%
Item 22. (Job) summed score	3.03 (1.90)	1-6	1	6
Item 22. transformed score	40.67 (38.05)	0-100%	0%	100%
Item 24. (Sexual function) summed score	2.67 (1.90)	1-6	1	6
Item 24. transformed score	33.33 (29.87)	0-100%	0%	100%
Item 25. (Intimate relationships) summed score	5.40 (1.07)	1-6	2	6
Item 25. transformed score	88.00 (21.40)	0-100%	20%	100%

The factor weights for all variables exceeded the minimum expected value of 0.25, with the lowest communality being 0.384. The factor weights showed similar values to the results of the original validation study **(Table 8).**

Table 8. Factor weights, items and relability values measured on the pilot-testing of the 'pre-final' Hungarian version of PADQOL (n=30)

Factors	Factor weights of the Hungarian version (own results)
1. Faktor ***Társas kapcsolatok és interakciók***	
Az érszűkületem nagyon megnehezíti az életemet.	0.794
Az érszűkületem nagy teher a számomra.	0.793
Az érszűkületem miatt elszigeteltnek érzem magam.	0.724
A családomra is kihat az érszűkületem.	0.712
Az érszűkületem nagyban korlátozza a szabadságomat.	0.681
Az érszűkületem nagyon megváltoztatta az életben betöltött szerepemet.	0.671
Az érszűkületem miatt úgy érzem, terhére vagyok másoknak.	0.582
Az érszűkületem miatt ért már valamilyen veszteség.	0.573
Az érszűkületem rossz hatással van a baráti kapcsolataimra.	0.512

2. Faktor ***Önkép és érzelmek***	
Az érszűkületem miatt nem érzem teljes értékűnek magam.	0.771
Nagyon kényelmetlenül érzem magam amiatt, hogy korlátoz az érszűkületem.	0.722 0.693
Amikor az érszűkületemre gondolok, tehetelennek érzem magam.	0.554
Úgy érzem, hogy az érszűkületem miatt nagyon sebezhető vagyok.	0.520
Úgy érzem, hogy az érszűkületem miatt már nem vagyok a régi.	0.490
Lehangol, amikor az érszűkületemre gondolok.	0.384
Nagyon félek attól, hogy másokra leszek utalva.	
3. Faktor ***Tünetek és testi funkcióbeli korlátozottság***	
Az érszűkületem miatt, sok olyan dolgot nem tudok csinálni, ami örömet okoz.	0,775 0,721
Az érszűkületem nagymértékben korlátozza a tevékenységeimet.	0.667
Az érszűkületem miatt, nem tudok annyit sétálni, mint amennyit szeretnék.	0.632 0.621
Járás közben nagyon fáj a lábam az érszűkületem miatt.	0.569
Az érszűkület sok fájdalmat okoz.	0.540
Nagyon zavar az érszűkületem	0.452
Nem tudok lépést tartani a kortársaimmal.	
Idősebbnek érzem magam a koromnál.	
4. Faktor ***Félelem és bizonytalanság***	
Félek, hogy el fogom veszíteni a lábam egy részét vagy az egész lábamat.	0.731 0.714
Félek, hogy az egészségi állapotom rosszabbodni fog az érszűkületem miatt.	0.519 0.421
Az érszűkületem folyamatosan rosszabbodni fog.	
Félek, hogy az érszűkületem miatt meghalok.	
5. Faktor ***Pozitív adaptáció***	
Tisztában vagyok az érszűletem okaival.	0.889
Sikerült úgy változtatnom az életemen, hogy jobban együtt tudjak élni az érszűkületemmel.	0.858
Minden szükségeset meg tudok tenni, hogy kézben tartsam a betegségemet.	0.807 0.801
Biztos vagyok benne, hogy megbirkózom mindennel, amit a jövő hoz.	0.759
Bizakodó vagyok az érszűkületemet illetően.	0.662
Javul az állapotom.	0.568
Az érszűkületem idővel fokozatosan javulni fog.	

We successfully carried out the linguistic validation and cross-cultural adaptation of the PADQOL self-reported quality of life questionnaire developed to measure the subjective burden of peripheral arterial disease into Hungarian and the completion of the pre-final version proved no difficulties. The linguistic validation process was conducted according to an internationally accepted and applied protocol. During the pilot-testing, we verified the clarity of the instructions, questions and response options of the questionnaire, modified one question based on the cognitive interviews and finalised the Hungarian version. At the pilot stage the Hungarian version of the questionnaire seemed reliable and

thus the validation process can proceed with the psychometric and clinicometric testing on a larger patient population. Upon completion of all stages of the validation process, the Hungarian version of PADQOL can be a useful tool in the assessment of the quality of life of Hungarian PAD patients and also for the evaluation and monitoring of the efficacy of therapeutic interventions from the patient's perspective as well.

Discussion

To date, there has not been any validated, PAD-specific, quality of life questionnaire in Hungarian language for routine use in Hungary. After obtaining the validation permission, we performed the linguistic validation and cross-cultural adaptation of the PADQOL instrument according to an international protocol. Our aim was to provide a new instrument which would allow for a more precise assessment and evaluation of the subjective disease burden experienced by patients suffering from PAD, and also the efficiency of interventions and quality of life gained through patients' perspective as well. The sufficiently high Cronbach-α value of the 'pre-final' Hungarian version of PADQOL and the high factor weights, which are similar to those published in the American study, prove that the translated instrument is reliable [22].

Kolossváry and his colleagues conducted a retrospective cohort study between 2004 and 2012, covering the whole of Hungary, using data retrieved from the Hungarian Central Statistics Office and EUROSTAT. The authors investigated the changes in the number of major lower limb amputations (above the ankle) performed as a consequence of PAD and unfortunately, found that the number of major lower limb amputations in Hungary did not change during the 9 years studied and that it was also alarmingly high compared to the European standard population (ESP). In the 9 years studied, 38,200 major amputations were performed in Hungary, with an incidence rate of 42.3/100,000 in the total population. 50.4% of patients who underwent amputation had diabetes [9]. The 2018 VASCUNET report also highlights the very high incidence of major amputations due to PAD in our country. In the age group ≥65 years, Hungary had the highest rate of major amputations compared to the total population (41.4/100,000), the highest amputation-related mortality rate (20.3%), and the highest rate of active smokers (25.8%) [10].

In clinical medical practice, quality of life is assessed and evaluated in terms of the short- and long-term impact of a disease and its treatment on patients' physical well-being, activity levels, interpersonal relationships and mental health. Long-term ill health can be tragic for the individual in many ways, not only due to the physical consequences of the disease itself (e.g. pain), but also because it can considerably hinder work and may negatively impact social life. For example, they may have difficulties in forming and maintaining social relationships. The disease, therefore, not only places a burden on the individual and society in terms of reduced physical functioning, but also negatively affects

the sense of 'competence' in other areas of life, which can significantly reduce subjective quality of life and lead to further deterioration in health [71].

As life expectancy increases, individuals live more and more years with chronic disease, which significantly impacts their quality of life. The prevalence and incidence of PAD also increase significantly with age. In the 60-70 agegroup, the increase is > 10% [4, 74].

Changes in disease-specific quality of life have been researched from various perspectives using several different instruments [18, 19]. Quality of life studies are an important input for health economic (cost-benefit) analyses of different health technologies and for disease burden assessments [90, 91, 92, 93, 94].

Generic questionnaires assess dimensions that are subjectively important for most people in relation to a particular illness (psychological and social well-being, performance, physical limitations). The SF-36 questionnaire, for example, provides a quality of life profile, while the EuroQol questionnaire allows the calculation of an aggregated quality of life indicator. Disease-specific questionnaires examine the specific problems relevant to a particular disease. With regard to PAD, the Vascular Quality of Life (VASQUQOL) includes 25 items that assess social and emotional well-being, pain, symptoms and activity, while the Walking Impairment Questionnaire (WIQ) focuses on pain and disability experienced in a patient's everyday life including daily walking distances, walking speed, walking distance and complaints experienced when climbing stairs but does not assess the psychosocial impact of PAD [78, 95, 96]. It has been proven that quality of life research requires the joint administration of generic and disease-specific questionnaires [72, 73]. In 2005, de Vries and colleagues conducted a prospective, multicentric study including 450 PAD patients to assess quality of life and found that their disease-specific questionnaire, the Vascular Quality of Life (VASCOQOL), differentiated mild versus severe peripheral arterial disease better than the general quality of life questionnaire (SF-36, EUROQoL-5D), and VASQUQOL was also found to be a more accurate measure of the quality of life of patients after therapeutic interventions (conservative therapy 143, percutaneous transluminal angioplasty 152 and surgical intervention in 91 patients) at the end of the 6-month follow-up period. [20].

Several studies have been conducted to assess the quality of life and burden of disease in peripheral arterial disease patients. In our country, Balogh et al. conducted a cross-sectional questionnaire survey in 4 angiology centres in Hungary involving a total of 102 patients using the EUROQoL-5D general quality of life measure to assess the quality of life and burden of disease in peripheral vascular patients with Fontaine stages II-IV. As a

result of their study, authors found that more advanced disease (Fontaine stage IV), the presence of resting ischaemic pain and ulcer, was associated with a significant deterioration in quality of life. Quality of life associated with PAD deteriorates along Fontaine stages [27].

Peripheral arterial disease represents a significant burden for both those affected and their environment as well as for society. A full understanding of the burden of disease associated with PAD, the measurement of gains in quality of life achieved by interventions, the prevention of the associated risks, and the reduction of the prevalence of minor and major amputations are of pivotal importance in our country, for which the PADQOL questionnaire can be a useful tool subsequent to psychometric and clinicometric testing.

We have created the final Hungarian version of the PADQOL questionnaire, a valid and reliable instrument for the next step of linguistic and cross-cultural adaptation, to assess the quality of life, subjective burden of disease, and the effectiveness of pharmacological therapy or surgical interventions in patients with PAD by psychometric and clinicometric assessment on a larger patient population.

6. DISEASE-SPECIFIC QUALITY OF LIFE AMONG PATIENTS WITH PERIPHERAL ARTERY DISEASE IN HUNGARY[4]

Peripheral artery disease (PAD) is a progressive atherosclerotic disease significantly impacting functional status and health-related quality of life (HRQoL). This study aimed to investigate HRQoL among PAD patients in Hungary using the validated Hungarian version of the PADQoL questionnaire. Patients with symptomatic PAD were consecutively recruited from the Department of Angiology, Clinical Center, University of Pécs, Hungary. Demographics, risk factors, and comorbidities were registered. Disease severity was measured by Fontaine and WIFI stages. Descriptive statistical analysis, Chi-square test, and non-parametric tests were performed ($p < 0.05$). Overall, 129 patients (mean age 67.6 ± 11.9 years, men 51.9%) participated in our study. The Hungarian PADQoL demonstrated good internal consistency (α range: 0.745–0.910). Factors on intimate and social relationships gave the best (89.15 ± 20.91; 63.17 ± 26.05) and sexual function (28.64 ± 27.42), and limitations in physical functioning (24.68 ± 11.40) the worst scores. PAD had a significant negative impact on the social relationships of patients aged 21–54 years (51.6 ± 25.4). Fontaine stage IV patients experienced significantly lower HRQoL due to fear and uncertainty (46.3 ± 20.9) and limited physical functioning (33.2 ± 24.8). The Hungarian PADQoL identified central aspects of HRQoL. Advanced PAD was found to impact several areas of HRQoL, primarily physical functioning and psycho-social well-being drawing attention to the importance of early diagnosis and management.

4 The chapter is based on the article:
***Horváth L,** Boncz I, Kívés Zs, Fehér G, Németh N, Kajos LF, Biró K, Fendrik K, Koltai K, Késmárky G, Endrei D. Disease-specific Quality of Life among Patients with Peripheral Artery Disease in Hungary. Int. J.Environ. Res. Public Health, 2023; 20(4) 3558.*

Introduction

Past decades have seen non-communicable diseases (NCDs) emerging as leading causes of morbidity and mortality worldwide, associated with an increasing disease burden in developing and developed regions alike. As cardiovascular diseases have become the main causes of mortality and morbidity, the prevalence of peripheral artery disease (PAD) has also been rising markedly [1, 2, 24]. According to most recent estimates, 236.62 million people above 25 years of age were living with PAD in 2015 [8].

Peripheral artery disease is a progressive atherosclerotic disease that results in stenosis or obstruction of the peripheral arteries and is an indicator of generalized atherosclerosis [3, 4, 25]. The presentation of PAD varies considerably, with many patients remaining asymptomatic for a while or experiencing only mild symptoms. Individuals with early stage PAD either do not experience or frequently under-report claudication symptoms (pain in the lower extremities triggered by walking due to reduced blood supply), and despite the high in-hospital costs associated with advanced stage PAD, the disease often remains undetected and untreated [33, 34, 35, 92, 94]. Symptomatic patients may experience claudication, cramping pain in the calves, thighs or buttocks, characteristically related to exercise such as walking or stair climbing, usually subsiding with rest. Further symptoms may also include atypical pain on exertion and ischaemic pain at rest. Untreated or advanced stage PAD may lead to tissue loss and amputation.

Risk factors for PAD include age, race, smoking, hypertension, diabetes, and hyperlipidaemia [97, 98, 99]. PAD is associated with considerable physical and psychosocial disease burden, primarily resulting from impaired functional status and quality of life [11, 12, 72, 100, 101] Studies conducted in the USA and Hungary have highlighted that functional impairment and pain resulting from lower extremity arterial ischaemia leads to reduced quality of life, and consequently, a considerable proportion of PAD patients experience severe symptoms of anxiety and depression. Studies have found that it is mainly impaired the lower extremity functioning that lies at the root of an impaired psycho-emotional state, considerably affecting engagement in social activities and family life [6, 7]. Mental health concerns, especially stress, are highly prevalent among PAD patients experiencing new or worsening symptoms. Higher stress levels have been shown to impede successful disease management [102]. Despite advanced endovascular and surgical limb salvage interventions becoming more available, the incidence of PAD-

related major and minor amputations has continued to remain alarmingly high, especially, in Eastern European countries, with Hungary continuing to have the highest rates [10, 63]. In spite of increasing efforts, PAD has continued to be underdiagnosed and undertreated [33, 32, 68]. As the past decades have seen a considerable rise in the number of multinational and multicultural research projects, the use of health-related quality of life (HRQoL) instruments in these studies, and consequently, the need to translate and adapt these health status measures for use in other than the source language has also grown rapidly. The increasingly international nature of drug trials has created a demand for translated instruments, primarily to enable a comparison or aggregation of results across different language groups. In terms of health policy, there is a need for indicators that can be used in monitoring the health of populations and for program evaluation. Increasing attention is also being paid to cross-cultural comparisons of effective interventions and preferences for different states of health in order to facilitate the extrapolation of results from effectiveness and cost-effectiveness studies from one country to the other [103] Besides traditionally used clinical outcome measures for evaluating the impact of a certain medical condition as well as the effects of invasive procedures, recent decades have seen a considerable increase in the application of generic and disease specific HRQoL questionnaires. Although clinical outcome measures in PAD including walking capacity (e.g. treadmill testing), physiological measurements such as the ankle-brachial index (ABI), patency tests of revascularized segments, or amputation-free survival provide an adequate and clear picture of the patients' objective clinical status, HRQoL measures, patient reported outcomes tools have been proven to add valuable information about the actual daily functioning of PAD patients. Furthermore, disease specific HRQoLs that have been developed and constructed to assess changes in the quality of life in subpopulations of patients suffering from a particular medical condition can assess the social and emotional consequences of living with a particular disease or help compare HRQoL prior to and after particular therapeutic interventions. It has been suggested that both generic and disease-specific questionnaires are required in quality of life research [73, 84]. Disease-specific questionnaires have been found to be able to discriminate more precisely between major versus more minor changes in disease severity, subsequent to interventions in PAD [20]. As Hungary has seen an alarmingly high level of major amputations related to PAD, our aim was to provide a further validated tool that can assess the subjective disease burden of patients with PAD experience. Peripheral artery disease quality of life (PADQoL) is a validated questionnaire, designed to assess disease-specific physical, psychosocial, and

emotional effects of PAD [22]. We aimed to assess the quality of life among patients suffering from various stages of PAD using the Hungarian version of the PADQoL questionnaire we have previously validated.

2. Materials and Methods: The type of research conducted was a quantitative cross-sectional study. The study was carried out at the Department of Angiology, 1st Department of Internal Medicine, Clinical Center, University of Pécs, Hungary. The study was conducted between March 2020 and November 2021. Patients were consecutively enrolled through purposive sampling. Informed consent was obtained from the study participants prior to completing the survey.

2.1. Data Collection Instrument: **PADQoL.** PADQoL is a disease-specific questionnaire developed by Treat-Jacobson et al. with the aim to provide a further validated tool for the assessment and evaluation of the impact of PAD on HRQoL from the aspect of subjective burden of disease. The 38-item questionnaire investigates five factors: social relationships and interactions (nine items), self-concept and feelings (seven items), symptoms and limitations in physical functioning (eight items), fear and uncertainty (four items), positive adaptation (seven items), and contains three individual items relating to job, sexual function, and intimate relationships. Response options were scored on a 6-point Likert-type scale ranging from 1 (strongly agree) to 6 (strongly disagree). Two of the individual items (sexual function, intimate relationships) and the summed scores on Factor 5 were reverse coded. The developers' aim was to construct an instrument that, aside from limitations in physical functioning, focused more on the subjectively perceived social and emotional burden of PAD and its effects on well-being and quality of life. PADQoL is different from other existing PAD-specific health-related quality of life instruments (e.g. the WELCH (Walking Estimated-Limitation Calculated) by History questionnaire that has been used to assess walking limitation in a PAD patient population in Hungary) [84] in that it is able to assess the relative differences for the individual patient, and may thus provide effective guidance to clinicians in choosing treatment strategies and help identify patients who may require additional therapies including psychotherapy or social support [22].

2.2. The Cross-Cultural Adaptation Process: The linguistic validation of self-administered health-related quality of life (HRQoL) questionnaires requires a unique method to ensure both linguistic and cultural equivalence between the original source (SL)

and target language (TL) versions. The linguistic validation of PADQoL was carried out according to international guidelines [21, 75, 88] as follows: two certified translators translated the questionnaire including the introduction, items, and response options from English into Hungarian. The so called 'informed' translator was specialized in medical and health-sciences translation and interpreting, and the other translator, the 'uninformed' translator, had a post-graduate certificate in economics and social sciences translation and interpreting. The 'informed' translator received information about the aim of the questionnaire and the concepts it was designed to investigate. As PADQoL is a self-administered health status measure, the two forward translators were recommended to focus more on maintaining a conceptual dynamic rather than formal equivalence. A third certified translator reviewed the two forward translations (T1 and T2) with the two forward translators, discussed inconsistencies, and agreed upon a consensus version (T3). Working from the consensus version (T3), totally blind to the original, two back translators with a non-medical background created two back translations. Back translators were native speakers of English, had been living in Hungary for more than 30 years, and were fluent in Hungarian. The back translations did not reveal gross inconsistencies or conceptual errors. A consensus team consisting of the forward translators, the back translators, the third consensus translator, two internist-angiology specialist physicians, a linguist, and an applied linguist reviewed and discussed all translations. The team reached a consensus on discrepancies and created the pre-final Hungarian version of PADQoL, which then underwent pilot-testing through cognitive interview sessions involving 30 patients. The pilot patient population consisted of native speakers of Hungarian who adequately represented the target population socio-demographically and clinically in terms of age, sex, education, diagnosis, and previous interventions including revascularization and comorbidities. None of the Hungarian items proved difficult to understand or were inappropriate at a conceptual level. Minor changes were necessary in the wording of the items' linguistic aspects and results of the pilot testing have been previously published [104, 105].

2.3. The Study Population: 129 patients from in- and outpatient care were involved in the study. Participants (males, females) with established diagnosis of PAD (Fontaine II–IV), aged 18 and above, who agreed to participate in the research and were able to fill in the questionnaires independently, were included. There was no upper age limit; patients who were unable to complete the questionnaire due to their mental or physical condition were

excluded. Fontaine stage I patients were also excluded from our study as the instrument used for measuring disease-specific quality of life was developed and designed for surveying patients living with symptomatic PAD. Patients who had lower leg ulcer (Fontaine IV) not only due to PAD but also due to chronic venous insufficiency were also excluded. Informed consent was obtained from the study participants prior to completing the survey. Participation was voluntary. All patients completed a paper-based PADQoL instrument during a face-to-face interview independently. Demographics included were gender, age, and educational achievement. Risk factors and comorbidities included body mass index (BMI), smoking, diabetes, hypertension, dyslipidemia, coronary heart disease, stroke/TIA, carotid artery narrowing, chronic kidney disease, chronic obstructive pulmonary disease (COPD), musculoskeletal disorders, and previous revascularization. Physical examination, resting ankle-brachial index (ABI) ≤ 0.9 was used as an indicator of disease. In patients with borderline ABI (0.90–1.00), further diagnostic tests were carried out as normal ABI does not definitely rule out the diagnosis of LEAD; in such cases, post-exercise ABI and Doppler ultrasonography were performed. In the case of a high ABI (>1.40) due to medial calcification, toe pressure and toe-brachial index (TBI) were measured [5]. The severity of patients was evaluated with the Fontaine and the WIfI classification systems. The Fontaine Classification system assesses the clinical presentation of patients, that is, symptoms ranging from asymptomatic PAD to the presentation of necrosis and/or gangrene in the lower extremities, and four stages are established indicating disease severity [106]. The WIfI classification system covers the three most essential parameters that may indicate the risk of a future amputation: wound, ischemia, and the presence of foot infection. This classification system attributes a 4-grade scale to each parameter, ranging from 0 to 3, where 0 represents absent, 1 mild, 2 moderate, and 3 severe risk [107, 108].

2.4. Statistical Analysis: Descriptive statistical methods were used, and the mean ± SD (standard deviation), absolute and relative frequency were calculated. To examine the association between categorical variables Chi-square test, in the case of continuous variables, the normality test (Shapiro–Wilk test) was performed on data presenting non-normal distribution, and nonparametric tests were carried out (Mann–Whitney U test, Independent samples KruskalWallis test with pairwise comparisons) at the 95% confidence interval (CI), ($p < 0.05$). Data analysis was performed using SPSS (version 22.0, IBM).

2.5. Ethical Approval The study was approved by the Regional and Institutional Research Ethics Committee of the Clinical Center of the University of Pécs (8106-PTE 2019).

3. Results

3.1. Sociodemographic Characteristics of Patients: A total of 129 patients completed our questionnaire survey, 62 women (48.1%) and 67 men (51.9%). The mean age was 67.6 years, SD 11.9 years, with a median of 70 years. The youngest participant was 21, the oldest was 89 years old. There was no significant difference between the sexes in the different age groups ($p = 0.950$). Regarding educational achievement, there were significantly more women among the participants with primary education only (28.4%; $p = 0.027$). There was no significant difference among the age groups regarding educational background ($p = 0.244$). With regard to smoking, 32 participants (24.8%) never smoked, 73 (56.6%) were past smokers, and 24 patients (18.6%) were current smokers. There was no significant difference between the sexes in terms of smoking ($p = 0.211$), although we found a higher percentage of women (22.4%) compared to men (14.5%) among the current smokers. Compared to educational achievement, no significant difference was found regarding smoking ($p = 0.605$), although there were more current smokers (28.0%) among those participants who only had an elementary education background compared to those who completed secondary (18.1%) or higher education (9.5%). The mean BMI in our study population was 27.8 kg/m2, SD: 6 kg/m2; median: 27.3 kg/m2. The average BMI among males was 28.5 kg/m2 (SD: 5.6 kg/m2) and among women 27.0 kg/m2 (SD: 6.3 kg/m2); we found no significant difference between the sexes ($p = 0.174$). We found no significant differences in the BMI when comparing age groups ($p = 0.492$), sexes ($p = 0.302$), or educational background ($p = 0.785$). Comparing the BMI categories with smoking yielded no significant differences either ($p = 0.239$). Considering the risk factors, 38% (49/129) were overweight, 29.4% (38/129) of participants were obese, and 18.6% (24/129) patients were current smokers. More than half of the patients (55.0% (71/129) of patients) had a diagnosis of diabetes, the majority of patients (88.4% (114/129)) had hypertension, and 89.1% (115/129) had dyslipidemia. Regarding comorbidities, 65.9% (85/129) of our participants had coronary heart disease (CHD), 50.4% (65/129) had carotid artery stenosis, 27.1% (35/129) suffered from chronic kidney disease, 17.8% (23/129) had had a stroke or transitory ischemic attack (TIA), 16.3% (21/129) had COPD, and 64.3% (83 patients) suffered from a musculoskeletal disorder. More than half of the study population (56.6%) had undergone previous revascularization (bypass or endovascular therapy) **(Table 9)**.

Table 9. Sociodemographic data, risk factors and comorbidities of the study population.

Variables	Total n (%)	Males n (%)	Females n (%)	p-values[a]
Age groups				
21-54 years	18 (14.0)	8 (12.9)	10 (14.9)	0.950
55-64 years	13 (10.1)	7 (11.3)	6 (9.0)	
65-74 years	59 (45.7)	29 (46.8)	30 (44.8)	
75 years and above	39 (30.2)	18 (29.0)	21 (31.3)	
Educational background				
less than 8 years of primary school/primary school certificate	25 (19.4)	6 (9.7)	19 (28.4)	**0.027***
Secondary school certificate	83 (64.3)	45 (72.6)	38 (56.7)	
Higher education degree	21 (16.9)	11 (17.7)	10 (14.9)	
RISK FACTORS, COMORBIDITIES				
Smoking				
never	32 (24.8)	13 (21.0)	19 (28.4)	0.211
past smoker	73 (56.6)	40 (64.5)	33 (49.3)	
current smoker	24 (18.6)	9 (14.5)	15 (22.4)	
BMI				
underweight (≤18.49 kg/m^2)	7 (5.4)	2 (3.2)	5 (7.5)	0.412
normal (18.50-24.99 kg/m^2)	35 (27.1)	14 (22.6)	21 (31.3)	
overweight (25.00-29.99 kg/m^2)	49 (38.0)	28 (45.2)	21 (31.3)	
obesity grade I.(30.00-34.99 kg/m^2)	23 (17.8)	10 (16.1)	13 (19.4)	
obesity grade II. (≥35.00 kg/m^2)	15 (11.6)	8 (12.9)	7 (10.4)	
Diabetes				
no	58 (45.0)	26 (41.9)	32 (47.8)	0.506
yes	71 (55.0)	36 (58.1)	35 (52.2)	
High blood pressure				
no	15 (11.6)	8 (12.9)	7 (10.4)	0.664
yes	114 (88.4)	54 (87.1)	60 (89.6)	
Dyslipidaemia				
no	14 (10.9)	6 (9.7)	8 (11.9)	0.680
yes	115 (89.1)	56 (90.3)	59 (88.1)	
Coronary heart disease				
no	44 (34.1)	21 (33.9)	23 (34.3)	0.956
yes	85 (65.9)	41 (66.1)	44 (65.7)	
Stroke / TIA				
no	106 (82.2)	52 (83.9)	54 (80.6)	0.627
yes	23 (17.8)	10 (16.1)	13 (19.4)	
Carotid artery narrowing				
no	64 (49.6)	33 (53.2)	31 (46.3)	0.430
yes	65 (50.4)	29 (46.8)	36 (53.7)	
Chronic kidney disease				
no	94 (72.9)	47 (75.8)	47 (70.1)	0.470
yes	35 (27.1)	15 (24.2)	20 (29.9)	
COPD				
no	108 (83.7)	50 (80.6)	58 (86.6)	0.363
yes	21 (16.3)	12 (19.4)	9 (13.4)	
Musculoskeletal disorder				
no	46 (35.7)	27 (43.5)	19 (28.4)	0.072
yes	83 (64.3)	35 (56.5)	48 (71.6)	
Previous revascularisation				
no	56 (43.4)	26 (41.9)	30 (44.8)	0.745
yes	73 (56.6)	36 (58.1)	37 (55.2)	

3.2. Severity of PAD: Less than one third of patients had Fontaine stage IIa (37/129; 28.7%), or IIb PAD (38/129; 29.5%), 14 participants (10.9%) suffered from stage III disease and every third patient had severe, stage IV PAD (40/129; 30.1%) **(Table 10)**. WIFI values, indicating amputation risk within a year, were calculated for patients with Fontaine stage III and stage IV disease. Out of the 54 patients who met this criterion according to the WIfI categories, 3.7% (2 patients) had very low, 22.2% (12 patients) had low, 18.5% (10 patients) had moderate, and more than half, 55.6% (30 patients), had a high risk for possibly having to undergo an amputation in the near future **(Table 11).** The number of volunteers in the Fontaine III group (N = 14) and WIFI groups 'very low' (N = 2) and 'high' (N = 30) were outliers.

Table 10. Fontaine stages in the study population (n=129).

Fontaine stages	**Nr of patients**	**Distribution (%)**
IIa	37	28.7
IIb	38	29.5
III	14	10.9
IV	40	31.0
Total	*129*	*100*

Table 11. Wifi categories in the study population (n=54).

Wifi category	**Nr of patients**	**Distribution (%)**
very low	2	3.7
low	12	22.2
moderate	10	18.5
high	30	55.6
Total	***54***	***100***

Table 12 provides a summary of the mean, standard deviation, possible range, and minimum and maximum scores for this sample. Item 24 'Intimate relationships' and Factor 1 'Social relationships and interactions' gave the highest (i.e. the best) scores. The worst (lowest) scores were found in the case of Item 23' Sexual function', and the Factors 'Symptoms and limitations in physical functioning' and 'Fear and uncertainty'.

Factor weights exceeded the minimum value of 0.25 in all variables. Factor weights were very similar to those of the original questionnaire (not shown in table).

Table 12. PADQoL questionnaire survey results.

PADQOL Factors	mean (SD)	Possible range	Minimum	Maximum
Factor 1. Social relationships and interactions, summed score	37.43 (11.72)	9-54	12	54
Factor 1. Social relationships and interactions, transformed score	63.17 (26.05)	0-100%	7	100
Factor 2. Self-concept and feelings, summed score	26.24 (9.58)	7-42	7	42
Factor 2. Self-concept and feelings, transformed score	54.97 (27.38)	0-100%	0	100
Factor 3. Symptoms and limitations in physical functioning summed score	24.68 (11.40)	8-48	9	48
Factor 3. Symptoms and limitations in physical functioning transformed score	41.37 (28.50)	0-100%	3	100
Factor 4. Fear and uncertainty summed score	14.88 (5.03)	4-24	6	24
Factor 4. Fear and uncertainty transformed score	54.42 (25.18)	0-100%	10	100
Factor 5. Positive adaptation summed score	26.09 (5.07)	7-42	9	35
Factor 5. Positive adaptation transformed score	54.55 (14.50)	0-100%	6	80
Item 21 Job summed score	3.87 (1.95)	1-6	1	6
Item 21 Job transformed score	57.36 (39.00)	0-100%	0	100
Item 23 Sexual function summed score	2.40 (1.32)	1-6	1	6
Item 23 Sexual function transformed score	28.64 (27.42)	0-100%	0	100
Item 24 Intimate relationships summed score	5.46 (1.04)	1-6	1	6
Item 24 Intimate relationships transformed score	89.15 (20.91)	0-100%	0	100

The reliability of the PADQoL subscales was assessed through calculating the Cronbach's alpha values ranging between 0.745 and 0.910 in our patient population. The internal consistency of the majority of the factors was excellent. Internal consistency values were the highest in Factor 1 and the lowest in Factor 5, similar to those of the original measure. The Cronbach's alpha values of the validated questionnaire were very similar to those of the original questionnaire, which proves that the translated Hungarian tool is reliable and measures selected aspects of HRQoL adequately **(Table 13.)**.

Table 13. PADQoL internal consistency of the final Hungarian version compared to the original version.

PADQOL factors	Cronbach's alpha **n=129**	Cronbach's alpha **n = 297** ***Treat-Jacobson et al., 2012***
Factor 1. Social relationships and interactions	**0.91**	0.92
Factor 2. Self-concept and feelings	**0.91**	0.89
Factor 3. Symptoms and limitations in physical functioning	**0.90**	0.88
Factor 4. Fear and uncertainty	**0.78**	0.80
Factor 5. Positive adaptation	**0.74**	0.73

Sex and educational achievement showed no significant correlation with any of the factors. Regarding age groups, patients aged 21–54 had significantly lower average scores in the Factor 'Social relationships and interactions' (F1) than those aged 65–74 years. Participants aged 75 years and above had significantly worse scores in Factors 'Positive adaptation' (F5) and 'Sexual function' (F7) compared to those between 21–54 and 65–67 years. The factor measuring work performance, 'Job' (F6), showed that compared to the younger age spectrum (21–54-year-old participants), those aged 65–74 and ≤75 years had significantly higher scores. Item 24 'Intimate relationships' showed high scores in all age-groups, in both sexes and was not significantly affected by educational background either. Item 23 measuring sexual function showed that the worst mean values significantly deteriorated above age 64 compared to the younger age groups. The Factor 'Symptoms and limitations in physical functioning' also indicated worse quality of life in our study population but showed no significant differences with regard to age, sex, or educational

background. Patients aged 21–54 years reported their social relationships and interactions to be more negatively impacted by PAD compared to those aged between 65 and 74 years. Positive adaptation was found to significantly deteriorate with age above 65 years. Item 21, measuring the impact of PAD on patients' work, revealed worse quality of life in this respect among younger patients. Item 24, assessing 'Intimate relationships', gave the highest mean values **(Table 14)**.

Table 14. Correlation between mean values of PADQoL factors with sociodemographic data.

*Legend: *Asterisked data indicate statistically significant results.*

Variables	N	F1 Social relationships and interactions	F2 Self-concept and feelings	F3 Symptoms and limitations in physical functioning	F4 Fear and uncertainty	F5 Positive adaptation	Item 21 Job	Item 23 Sexual function	Item 24 Intimate relationships
All patients	129	63.2±26.1	55.0±27.4	41.4±28.5	54.4±25.2	54.6±14.5	57.4±39.0	28.6±27.4	89.2±21.0
Sexes									
males	62	63.5±24.8	55.1±27.3	39.8±28.6	52.1±26.2	56.5±13.1	56.7±40.0	28.0±26.4	91.3±16.0
females	67	62.8±27.7	54.8±27.6	43.5±28.4	56.6±24.2	52.7±15.5	57.9±38.3	27.8±26.5	87.2±24.5
p-values[b]		0.940	0.979	0.445	0.285	0.201	0.996	0.889	0.505
Ages									
21-54 years	18	**51.6**±26.4	48.7±27.7	31.1±28.3	51.7±26.4	**61.9**±9.0	26.7±40.9	**45.6**±35.5	93.3±13.7
55-64 years	13	70.7±20.2	62.8±20.3	43.0±29.0	47.6±24.2	55.8±12.6	**35.4**±40.9	52.3±23.8	86.1±28.7
65-74 years	59	**68.4**±25.6	59.0±28.1	47.6±27.3	58.7±24.2	**55.7**±14.2	**66.4**±34.9	**26.1**±24.1	87.1±23.1
>75 years	39	58.0±26.3	49.0±27.2	37.8±29.2	51.4±26.1	**49.0**±15.9	**65.1**±34.5	**14.3**±13.7	91.2±17.0
p-value[sa]		**0.040***	0.177	0.085	0.354	**0.011***	**<0.001***	**<0.001***	0.657
Educational background									
less than 8 years of primary school / primary school certificate	25	61.9±25.4	53.6±30.0	37.9±25.6	52.0±24.6	52.2±15.0	52.0±38.7	28.0±24.4	94.4±10.8
secondary school certificate	83	62.1±25.9	54.9±26.5	41.9±29.6	54.7±26.2	54.2±14.5	56.6±39.4	27.9±26.1	88.2±21.4
college/university	21	63.2±28.3	56.9±28.5	45.5±28.0	55.9±22.4	58.6±13.6	69.7±37.5	27.6±31.3	86.7±27.0
p-value[a]		0.932	0.942	0.700	0.850	0.280	0.273	0.874	0.537

[a]Kruskal-Wallis test, [b]Mann-Whitney U test

Upon comparing Fontaine stages with the PADQoL subscales, we found that the mean values in Factors F1 and F3 decreased with disease severity. Factor F2 also showed a decrease with advancing PAD with Fontaine stage III and IV patients reporting significantly lower quality of life and increasing levels of inner fears and uncertainty compared to patients with stage IIa disease **(Table 15)**. Item 23, measuring sexual function, showed the impact of PAD on this segment of life early on and further decline. Factor F5 and Items 21 and 24 did not show significant change with advancing disease.

Table 15. The correlation between Fontaine stages and PADQoL factors.
*Legend: *Asterisked data indicate statistically significant results.*

Fontaine stages	N	F1 Social relationships and interactions	F2 Self-concept and feelings	F3 Symptoms and limitations in physical functioning	F4 Fear and uncertainty	F5 Positive adaptation	Item 21 Job	Item 23 Sexual function	Item 24 Intimate relationships
II.a	37	**77.9±18.6**	**65.7±25.2**	**57.7±27.7**	**64.5±25.8**	54.4±16.0	68.11±38.7	30.8±26.4	87.5±21.2
II.b	38	**59.3±28.9**	52.8±30.0	**38.9±29.4**	56.0±27.2	53.4±15.9	51.5±40.9	33.1±28.0	92.6±13.4
III.	14	**58.1±17.2**	57.3±20.3	**30.8±21.5**	**46.0±20.0**	58.9±13.2	50.0±37.4	28.5±29.0	97.1±7.2
IV.	40	**55.0±26.7**	**46.2±26.1**	**33.2±24.8**	**46.3±20.9**	54.0±12.0	55.5±37.2	20.0±23.0	84.5±27.7
p-value[a]		**<0.001***	**0.020***	**<0.001***	**0.011***	0.720	0.182	0.101	0.245

4. Discussion

We intended to investigate the HRQoL among patients suffering from PAD using a disease-specific quality of life instrument we had previously validated and cross-culturally adapted for use in Hungary. As the global burden of PAD has also increased over the past decades in developed and developing regions of the world, the early detection of the disease, especially among asymptomatic patients or those with atypical symptoms, is of crucial importance, as PAD has remained underdiagnosed and untreated [32, 68]. PAD is associated with significant morbidity and mortality from cardio- and cerebrovascular diseases and patients have an equal risk of suffering a future stroke or MI as patients with coronary artery disease [31, 109]. PAD is associated with considerable physical and psychosocial disease burden, primarily resulting from declining physical/functional status and deterioration in the quality of life [11, 12, 110]. Besides a healthy diet, physical activity and controlled exercise training, smoking cessation is one of the most important elements of CV risk factor management. Unfortunately, Hungary has not shown the desired levels of a reduction in smoking among the general population, which is also reflected by the fact that more than half of our participants were past, and nearly 20% were current smokers, despite having been diagnosed with PAD [69]. Lower levels of education were associated with higher rates of smoking. The fact that more than half of our patient population had diabetes, and a significant majority had hypertension and dyslipidemia underline the importance of early diagnosis and adequate pharmacological therapy including up-to-date lipid control (statin, ezetimibe) and adequate antiplatelet therapy [5]. As PAD is a sign of generalized atherosclerosis, it was not unusual to find that more than

half of our patients had CHD, or carotid artery narrowing. Previous stroke/TIA were also present in nearly one-fifth of our patients. Although our sample size was quite small, our findings emphasize the importance of a need for more complex screening for CVD events, especially among patients with asymptomatic disease [111]. Although more than half of the study population had undergone previous revascularization (bypass or endovascular therapy), Hungary and other Eastern European countries are in a 10-year delay with regard to these types of interventions being prioritized as the first-line option [9, 112]. The current sad situation is also highlighted by the fact that every third of our patients had severe, stage IV PAD, and more than half were at high risk of a future amputation. The PADQoL questionnaire survey results clearly demonstrated the impact of PAD on sexual and physical function, together with increased levels of anxiety and fear among patients suffering from the disease becoming more expressed with age. Our findings also underline the extent to which PAD impacts upon social life, interfering with friendships and aspects of social life function. Apparently, younger patients felt more severe limitations in terms of the social relationships caused by PAD as with age, and due to other comorbidities, older people tend to become used to being limited in their social lives. Intimate relationships were the least affected area of life, irrespective of age or disease severity, the majority of our patients reported as having been satisfied with this aspect of their lives, which underlines the importance of the support coming from close relationships with family and friends in coping with a progressive medical condition, especially as positive adaptation showed a considerable decrease in older patients in our study, and worse perceived health status has been shown to be associated with deteriorating mental health [113, 114]. The PADQoL factor measuring work performance showed that compared to the younger age spectrum, participants above 65 years scored significantly higher, emphasizing the fact that PAD progresses with age, and consequently, has a more severe impact on the ability to engage in work-related activities. Comparing the PADQoL factors with Fontaine stages underlined the fact that patients with more advanced PAD are increasingly hindered in keeping contact with friends and relations and in engaging in social activities mainly due to physical pain and the resulting limitations in movement. PAD has a strong impact on the patients' self-concept and self-worth, and significantly affects psychological well-being. Our survey also found a considerable decrease in this respect with advancing disease, with Fontaine stages III and IV patients reporting significantly lower quality of life and increasing levels of inner fears and uncertainty compared to patients with stage IIa disease. The above clearly demonstrate that PAD has a considerable impact upon multiple aspects

of psychological and social life, aside from significantly deteriorating the patients' physical health, as has been revealed by several previous studies [22, 39, 115, 116]. The number of volunteers in the Fontaine III group and WIfI groups 'very low' and 'high' were outliers, which might be a limitation of our study. Due to this reason, we provided subgroup analysis only according to Fontaine stages (Kruskal–Wallis test) and not for the WIfI categories. Finally, our study had some limitations. It was a cross-sectional, observational study in nature including more than 120 patients. The sample was not representative of the general PAD population. The fact that all patients were recruited from one regional clinical center may have resulted in some degree of selection bias. The above-mentioned limitations may have influenced our findings. Additionally, follow-up with regard to the effectiveness of medication therapy or revascularization procedures was not carried out.

5. Conclusions

Aside from validating and adapting a new HRQoL questionnaire for use in Hungary, our cross-sectional study measured the HRQoL among patients living with different stages of PAD. Our results revealed that PADQoL can be an effective tool in assessing the quality of life in the Hungarian patient population and could also be used for monitoring the change subsequent to pharmacotherapy or surgical interventions, thereby enabling the comparison of quality of life gained with international data. As our study revealed significant associations between more advanced stages of PAD (Fontaine III and IV) and HRQoL mainly in the areas of social life and mobility markedly impacting emotional health as well as highlighting the pivotal importance of early diagnosis and the adequate management of PAD patients.

7. DISCUSSION

With the aging of global populations people are expected to live longer years with chronic conditions that significantly impact quality of life. Our review on the epidemiology of PAD revealed a marked increase in the global disease burden associated with PAD all regions of the world has seen during past decades with developing regions of the world having witnessed a more pronounced increase in PAD-attributable disease burden. PAD has caused increasing burden on healthcare systems alike [1, 2, 24] as the management of PAD patients account for considerably high percentages of in-hospital and healthcare costs [32]. PAD is associated with significant morbidity and mortality from cardio- and cerebrovascular diseases and patients have an equal risk of suffering a future stroke or MI as patients with coronary artery disease [31]. PAD is associated with considerable physical and psychosocial disease burden primarily, due to impaired physical functioning and significantly impacted, deteriorating quality of life [11, 12, 39]. Despite advancing techniques and pharmacological treatment modelities PAD has remained underdiagnosed and undertreated [67, 68]. PAD-related major and minor amputations have not decreased at expected rates, especially in Eastern European countries (9, 10). Hungary has continued to show very high amputation rates, amputation-related mortality and PAD-related mortality [56]. As our major aim was to assess and evaluate quality of life among Hungarian patients living with PAD, we initially carried out the linguistic validation of PADQoL disease-specific HRQoL questionnaire according to an international protocol.

The linguistic validation of PADQOL into Hungarian posed no difficulties in terms of semantic, experiential and idiomatic equivalence. One item was found difficult to interpret during cognitive interviewing and was thus modified. The ‘pre-final’ version of the questionnaire was easy to understand and complete. Reliability of subscales and the internal consistency of items were good [103, 104, 105]. Our cross-sectional observational study including 129 patients using the previously validated questionnaire revealed the impact of PAD on multiple aspects of physical, and psycho-social well-being, including work perfomance, sexual and physical functioning, and levels of anxiety and fear. Advanced-stage disease was associated with worse quality of life in many respects which emphasises the importance of early diagnosis and treatment of PAD. By validating and

adapting a new HRQoL questionnaire for use in Hungary we provided a new, effective tool for the assessment of quality of life among Hungarian patients which could also be used for monitoring changes subsequent to pharmacotherapy or surgical interventions, and thus for comparison of international data on quality of life gained [117].

Healthcare suffers from an overabundance in metrics, and data for process measures, and while these are primarily intended to improve quality of care that patients receive across a country, they often fail to provide insight into how a particular disease and treatment impact patients' daily lives. PADQoL is a patient-reported outcomes measure (PROM) that proved useful in assessing disease-specific quality of life based on information coming directly from the patients. PROMs have become important tools in improving communiation between patients and their providers, thereby, facilitating shared decision-making by helping to deliver the most appropriate interventions in the best way possible while avoiding costly and unnecessary actions. Patient engagement and thus, quality of life indicators have become integral elements in cost-utility research influencing policy-making decisions in healthcare.

8. NOVEL RESULTS

Novel results discussed in the thesis are summarised as follows:

1. We provided an up-to date review on the epidemiology of peripheral artery disease from a global, international and national perspective highlighting the Hungarian situation.
2. We performed the linguistic validation and cross-cultural adaptation of PADQoL. disease-specific quality of life measure according to stages defined by international validation guidelines including: forward translation, consensus version, back translation, consensus meeting, pre-final Hungarian version of PADQoL.
3. We conducted the pilot testing of the pre-final Hungarian version of PADQoL through conducting cognitive interviews with patients living with PAD (n=30) and thereby created the final Hungarian version of the questionaire.
4. We investigated HRQoL among PAD patients in Hungary using the validated Hungarian version of the PADQoL questionnaire. Our cross-sectional study revealed significant associations between more advanced stages of PAD (Fontaine III and IV) and HRQoL and different areas of social life, mobility, and emotional health.

Practical implications:

1. We provided a further validated, self-report quality of life measure for everyday clinical use in Hungary that can assess the subjective disease burden patients with PAD experience.
2. Patient reported outcomes measures, and thus the new Hungarian PADQoL disease-specific questionnaire can help improve communication and shared-decision making between clinicians and patients, improving outcomes and patient satisfaction with care. PADQoL may prove to be an effective tool in monitoring disease progression and improvement in clinical and subjective disease status subsequent to pharmacological and surgical interventions.
3. Quality of life indicators are important input data in health-economic research, mainly in cost-utility analyses consequently, they markedly contribute towards and facilitate policy making decisions in health care.

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10. LIST OF PUBLICATIONS

PUBLICATIONS RELATED TO THE THESIS:

1. Horváth L, Elmer D, Németh N, Boncz I, Endrei D. Translation challenges during the linguistic validation of PADQoL (Peripheral Artery Disease Quality of Life) questionnaire into Hungarian. In: Vesna, Cigan; Ana-Marija, Krakić; Darija, Omrčen (eds.) IV. International Conference From Theory To Practice In Language For Specific Purposes. Conference Proceedings. Zagreb, Horvátország: Association of LSP Teachers at Higher Education Institutions 2019; pp. 60-70

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PARTICIPATION ON INTERNATIONAL CONFERENCES WITH PUBLISHED ABSTRACTS RELATED TO THE THESIS:

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11. APPENDICES

1.1. LINGUISTIC VALIDATION PERMISSION

LINGUISTIC VALIDATION PERMISSION

The undersigned, Prof. Diane Treat-Jacobson, co-developer and co-author of the Peripheral Artery Disease Quality of Life Questionnaire (PADQOL), hereinafter referred to as the "Author", hereby agrees to authorize Prof. Imre Boncz, Dr. Dóra Endrei and Lilla Horváth on behalf of the Institute for Health Insurance, Faculty of Health Sciences, University of Pécs, Hungary, hereinafter referred to as the "Users" to perform the full linguistic validation and cultural adaptation of PADQOL questionnaire into Hungarian according to standard recognized linguistic validation methodology.

The "Users" acknowledge the "Author's" copyright in the PADQOL questionnaire and in all its versions and shall not contest such copyright or perform any act or omission adverse to such exclusive right.

Upon completion, the "Users" shall provide the "Author" with the new translation in one standard exploitable format and one read-only file format (i.e. PDF), therefore allowing the "Author" to check whether the standard format has undergone any font or character modifications during possible conversions.

December 2018

Diane Treat-Jacobson

.....

Prof. Diane Treat-Jacobson Ph.D. R.N.

Signature

1.2. CONSENSUS MEETING

CONSENSUS MEETING

17TH April 2018

Having reviewed and consolidated translations (T1, T2, T3, BT1, BT2) of the original PADQOL questionnaire, the undersigned hereby agree, that the pre-final Hungarian version can undergo pilot testing.

Prof.Dr Boncz Imre (Supervisor)

Dr.Enderi Dóra (Supervisor)

Dr. Lehmann Magdolna (Methodologist)

Dr. Dombi Judit (Linguist)

Dr.Koltai Katalin (Internist, Angiologist)

Dr. Késmárky Gábor

(Internist, Cardiologist, Angiologist)

Fekete Adrienn (Forward Translator)

Baditz Mihály Bence (Forward Translator)

Vivian Brasch (Back Translator)

Dr. Andrew C. Rouse (Back Translator)

Horváth Lilla (PhD student, Project Coordinator)

Pécs, 17.04.2018

1.3. PADQoL Questionnaire Hungarian Version

Perifériás verőérbetegség életminőség kérdőív

Az alsó végtagi érszűkület hatása az életminőségre

A következő felsorolás olyan állításokat tartalmaz, amiket alsó végtagi érszűkületben szenvedő betegek fogalmaztak meg a problémáikról, érzéseikről. **Az alsó végtagi érszűkület (továbbiakban: érszűkület) a lábat ellátó artériák szűkülete.** Kérem, jelölje meg, milyen mértékben ért egyet a következő állításokkal. **Nincs jó vagy rossz válasz. Kérem, hogy minden állításra úgy válaszoljon, ahogy ma érzi magát:**

1. **Az érszűkületem nagymértékben korlátozza a tevékenységeimet.**

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

2. **Az érszűkületem miatt, nem tudok annyit sétálni, mint amennyit szeretnék.**

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

3. **Az érszűkületem miatt, sok olyan dolgot nem tudok csinálni, ami örömet okoz.**

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

4. **Járás közben nagyon fáj a lábam az érszűkületem miatt.**

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

5. **Idősebbnek érzem magam a koromnál.**

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

6. Az érszűkületem miatt ért már valamilyen hátrány, vagy veszteség.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

7. Félek, hogy el fogom veszíteni a lábam egy részét, vagy az egész lábamat.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

8. Félek, hogy az érszűkületem miatt meghalok.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

9. Az érszűkületem folyamatosan rosszabbodni fog.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

10. Nagyon zavar az érszűkületem.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

11. Félek, hogy az egészségi állapotom rosszabbodni fog az érszűkületem miatt.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

12. Javul az állapotom.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

13. A családomra is kihat az érszűkületem.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

14. Bizakodó vagyok az érszűkületemet illetően.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

15. Biztos vagyok benne, hogy megbirkózom mindennel, amit a jövő hoz.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

16. Sikerült úgy változtatnom az életemen, hogy jobban együtt tudjak élni az érszűkületemmel.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

17. Nem tudok lépést tartani a kortársaimmal.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

18. Az érszűkületem rossz hatással van a baráti kapcsolataimra.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

19. Amikor az érszűkületemre gondolok, tehetetlennek érzem magam.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

20. Tisztában vagyok az érszűkületem okaival.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

21. Az érszűkületem hatással van, vagy hatással volt a munkámra.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

22. Az érszűkület sok fájdalmat okoz.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

23. Nagyon elégedett vagyok a szexuális életemmel.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

24. Nagyon elégedett vagyok a közeli kapcsolataimmal.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

25. Lehangol, amikor az érszűkületemre gondolok.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

26. Az érszűkületem miatt nem érzem teljes értékűnek magam.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

27. Az érszűkületem nagyon megnehezíti az életemet.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

28. Az érszűkületem nagy teher a számomra.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

29. Nagyon félek attól, hogy másokra leszek utalva.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

30. Az érszűkületem miatt elszigeteltnek érzem magam.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

31. Az érszűkületem nagyban korlátozza a szabadságomat.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

32. Úgy érzem, hogy az érszűkületem miatt már nem vagyok a régi.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

33. Úgy érzem, hogy az érszűkületem miatt nagyon sebezhető vagyok.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

34. Minden szükségeset meg tudok tenni, hogy kézben tartsam a betegségemet.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

35. Nagyon kényelmetlenül érzem magam amiatt, hogy korlátoz az érszűkületem.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

36. Az érszűkületem idővel fokozatosan javulni fog.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

37. Az érszűkületem miatt úgy érzem, terhére vagyok másoknak.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

38. Az érszűkületem nagyon megváltoztatta az életben betöltött szerepemet.

1	2	3	4	5	6
Teljesen egyetértek	Egyetértek	Részben egyetértek	Részben nem értek egyet	Nem értek egyet	Egyáltalán nem értek egyet

1.4. ETHICAL APPROVAL

PÉCSI TUDOMÁNYEGYETEM
Klinikai Központ
Regionális és Intézményi Kutatás-Etikai Bizottsága

Horváth Lilla Anita
PhD hallgató
Postai cím: 7621 Pécs, Mária utca 47.
Vizsgálatvezető

Pécs, 2019. november 29.

Tisztelt Vizsgálatvezető!

A PTE-KK Regionális és Intézményi Kutatás – Etikai Bizottsága a **2019. november 29.**-ei ülésén megtárgyalta az Ön **által benyújtott** dokumentumokat

Témavezetők: dr. Endrei Dóra egyetemi docens
PTE KK I. számú Belgyógyászati Klinika Angiológiai Tanszék;
dr. Boncz Imre egyetemi tanár PTE ETK Egészségbiztosítási Intézet
PTE Egészségtudományi Doktori Iskola

Cím: A perifériás verőérbetegségben (PAD) szenvedő betegek életminőség vizsgálat

Sponzor: saját kezdeményezésű kérdőíves klinikai vizsgálat

Mellékletek: (1.) Kutatási tev irodalmi háttérrel; (2.) a klinikai adatok felhasználása miatt a PTE Egészségügyi Adatvédelmi Szabályzatának „10. számú mellékletét: Statisztikai és tudományos adatgyűjtési kérelem"-et a PTE KK elnökének aláírásával benyújtotta Bizottságunknek; (3.) Névreszóló szerzői engedély a kérdőív felhasználásához; (4.) SP-36 kérdőív az általános egészségi állapotról, illetve PADQOL betegségspecifikus kérdőív arról, hogy milyen hatással van a perifériás érbetegség az életvitelére, életminőségére; végső validált magyar fordítása PADQOL; (5.) Betegtájékoztató és beleegyező nyilatkozat; (6.) támogató nyilatkozat a klinika igazgatótól és témavezetőktől; (7.) a vizsgálatok helyszíne PTE KK I. számú Belgyógyászati Klinika Angiológiai Tanszék;

Döntés: a PTE KK RIKEB a **2019. november 29.-ei** ülésén **engedélyezte** a vizsgálatok protokoll szerinti kivitelezését. Egyúttal felkérjük a tisztelt vizsgálatvezetőt, hogy a klinikai vizsgálatok állásáról **évente**, lezárása után pedig **összefoglaló jelentést** legyen szíves küldeni Bizottságunk részére.

Ügyiratszám: 8106 – PTE 2019.

Szívélyes üdvözlettel

Dr. Kosztolányi György
egyetemi tanár, a Bizottság elnöke

Dr. Kocsis Béla
egyetemi docens, a Bizottság titkára

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PÉCSI TUDOMÁNYEGYETEM
OM azonosító FI 58544
Egészségtudományi Kar
Egészségtudományi Doktori Iskola

Pécsi Tudományegyetem
Klinikai Központ
Regionális és Intézményi Kutatás-Etikai Bizottsága

Pécs, 2019. január 23.
Tárgy: támogató nyilatkozat
Ikt.sz.: PTE/ 9910-1/2019

Prof. Dr. KOSZTOLÁNYI György
egyetemi tanár
elnök

Pécs
Rákóczi út 2.
7623

Tisztelt Elnök Úr!

Alulírott **Prof. Dr. Sulyok Endre**, mint az Egészségtudományi Doktori Iskola titkára támogatom **Horváth Lilla Anita** (szül.: Pécs; 197311.04.; anyja neve: dr. Wensofszki Ibolya Mária) **Ph.D hallgató**

„A perifériás verőérbetegségben szenvedő betegek életminőség vizsgálata (PADQOL betegség specifikus kérdőív validálása"

témájú klinikai kutatás protokoll szerinti kivitelezését.

Tisztelettel:

Prof. Dr. SULYOK Endre az MTA doktora
professor emeritus
az Egészségtudományi Doktori Iskola titkára

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Telefon/Fax: +36 (72) 513-678
e-mail: doktoriskola@etk.pte.hu•

1.5. PATIENT INFORMATION LEAFLET

BETEGTÁJÉKOZTATÓ
Kedves Betegünk!

A perifériás érbetegség egy gyakran előforduló érbetegség, amelyben a beszűkült verőerek csökkentik a végtagok – általában – az alsóvégtagok – vérellátását. A betegség kialakulásakor a vérellátás általában nem elegendő a szövetek szükségleteinek kielégítésére, és ez okozza a tüneteket.
A betegség súlyossága széles határok között mozoghat. A fájdalom lehet enyhe, de lehet akár a mozgást súlyosan korlátozó mértékű is. A perifériás érbetegség előrehaladásával a fájdalom nyugalomban vagy fekvéskor is jelentkezhet. A perifériás érbetegség leggyakoribb oka az érelmeszesedés, az érszűkület. A perifériás érbetegség minél korábbi felismerése és kezelése nemcsak a végtagok egészségének megőrzése miatt nagyon fontos, hanem a szívbetegség és a stroke kialakulásának megelőzésében játszik kiemelten fontos szerepet.
Kutatómunkám célja a perifériás érbetegek életminőségének vizsgálata.
Kutató munkám részekén két kérdőív kitöltésében szeretném a segítségét kérni. Az egyik kérdőív az Ön általános egészségi állapotáról kérdez, a másik a perifériás érbetegség által megélt testi, lelki panaszok, problémák súlyosságát vizsgálja mellyel azt szeretnénk megtudni, hogy milyen hatással van a perifériás érbetegség az Ön életére.
A kérdőívek kitöltése teljes mértékben önkéntes. A benne szereplő adatokat kizárólag tudományos célokra használom fel, és a válaszai nem lesznek beazonosíthatóak.
Kérem, hogy a lehető legőszintébben válaszoljon a kérdésekre. A kérdőívekben vannak hasonló kérdések, ennek elsősorban az az oka, hogy a kérdőív pontosan mérjen.
A kutatással kapcsolatos bármilyen jellegű kérdésével, örömmel állok rendelkezésére az alábbi email címen: lilla.horvath@etk.pte.hu

A kérdőívre szánt idejét, energiáját előre is köszönöm! Horváth Lilla PhD hallgató

_____	_____	_____
Vizsgálati alany aláírása	Dátum	Vizsgálati alany neve nyomtatott betűkkel

_____	_____
A tájékoztató és beleegyező beszélgetést lefolytató személy aláírása	A tájékoztató és beleegyező beszélgetést lefolytató személy aláírása nyomtatott betűkkel

1.6. DATA PROTECTION INFORMATION SHEET

ADATVÉDELMI TÁJÉKOZTATÓ

A kezelt adatok köre

- A kutatás során az alábbi adatok kezelésére kerülhet sor: pl.: születési év stb

A kutatás során az alábbi egészségügyi adatok kezelésére kerülhet sor**:** testsúly, testmagasság, dohányzás, cukorbetegség, dyslipidemia, stb.

Az adatkezelés célja

- Fenti adatait a kutatás adminisztrációjához, lebonyolításához, és az ezzel kapcsolatos tudományos és statisztikai elemzéshez fogják felhasználni, a vonatkozó jogszabályi rendelkezések figyelembevételével. Az adatkezelés célja összhangban van az Eüak. 4. § (2) bekezdés d) pontjával.

Az adatkezelés jogalapja
Miután a kutatás az Ön önkéntes hozzájárulása mellett folytatható csak le, az adatkezelés jogalapja is az Ön hozzájárulása lesz (GDPR 6. cikk. (1) bekezdés a) pont, valamint Infotv. 5. § (1) bekezdés a) pont).

Az adatkezelés időtartama

A kutatással összefüggő személyes adatait a Pécsi Tudományegyetem, illetve a kutatás során felvett és álnevesített adatait a PTE Egészségtudományi Doktori Iskola a kutatás lezárását követően a kutatási engedélyben, a jogszabályokban és a belső szabályzatokban rögzített meghatározott ideig őrzi meg.

Adattovábbítás
Az Ön személyes adatai nem kerülnek harmadik személyek, és más címzettek számára továbbításra.

Adatbiztonsági intézkedések
Annak érdekében, hogy illetéktelen személyek ne férjenek hozzá az adataihoz a jogszabályi, és belső szabályzatok előírásoknak megfelelően személyes adatait zártan kezeljük, az álnevesített adatokat pedig biztonságos elektronikus adatbázisban tároljuk.

1.7. DECLARATION OF CONSENT

BELEEGYEZŐ NYILATKOZAT

Klinikai vizsgálat neve: Perifériás verőérbetegségben szenvedő betegek életminőség vizsgálata (lingvisztikailag validált PADQOL betegség specifikus kérdőív és SF-36 generikus kérdőívvel)
Klinikai vizsgálat helyszíne: Pécsi Tudományegyetem Klinikai Központ I.sz Belgyógyászati Klinika, Kardiológiai és Angiológiai Tanszék
Vizsgálatvezető neve:
Önkéntesen beleegyezem jelen vizsgálatban való részvételbe. Körültekintően elolvastam, megértettem és teljeskörűen elmagyarázták nekem a vizsgálati tájékoztatóban szereplő információkat. Elegendő időt kaptam arra, hogy átgondoljam a vizsgálatban való részvételemet. Megértettem, hogy szabadon visszautasíthatom a vizsgálatban való részvételemet és, hogy e döntésem nem befolyásolja majd későbbi orvosi ellátásomat.
Megértettem, hogy kapok egy aláírt és keltezett példányt a beleegyező nyilatkozatból, amelyet megtarthatok.
A beleegyező nyilatkozat aláírásával semmilyen olyan törvényes jogomról nem mondok le, amely engem megilletne, ha nem vennék részt egy klinikai vizsgálatban.

_____		_____
Vizsgálati alany aláírása	Dátum	Vizsgálati alany neve nyomtatott betűkkel
_____		_____
Vizsgálati alany születési helye és ideje		Vizsgálati alany TAJ száma
_____		_____
A tájékoztató és beleegyező beszélgetést lefolytató személy aláírása		A tájékoztató és beleegyező beszélgetést lefolytató személy neve nyomtatott betűkkel

12. DECLARATION

Submission of the doctoral dissertation and declaration of the originality of the dissertation

Appendix 7

SUBMISSION OF THE DOCTORAL DISSETRTATION AND DECLARAITION OF THE ORIGINALITY OF THE DISSERTATION

The undersigned
name: HORVATH LILLA ANITA

maiden name: HORVATH LILLA ANITA

mother's maiden name: DR. WENSOFSZKI IBOLYA MÁRIA

place and time of birth: PÉCS, 1973. 11. 04.

on this day submitted my doctoral dissertation entitled

VALIDATION OF PERIPHERAL ARTERY DISEASE QUALITY OF LIFE QUESTIONNAIRE (PADQoL) AND MEASURING DISEASE-SPECIFIC QUALITY OF LIFE AMONG PATIENTS WITH PERIPHERAL ARTERY DISEASE

to the

programme/topic area PR-1 / E-77

of the HEALTH SCIENCES (D171) Doctoral School.

Names of the consultant(s): DR. HABIL. ENDRE DÓSA, PROF. DR. BOKOR IMRE

At the same time I declare that
- I have not submitted my doctoral dissertation to any other Doctoral School (neither in this country nor abroad),
- my application for degree earning has not been rejected in the past two years,
- in the past two years I have not had unsuccesful doctoral procedures,
- my doctoral degree has not been withdrawn in the past five years,
- my dissertation is independent work, I have not presented others' intellectual work as mine, the references are definite and full, on preparation of the dissertation I have not used false or falsified data.

Dated: 24. 10. 2023

H. Lilla

signed by candidate

supervisor

co-supervisor

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