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**DISCIPLINE OF MICROSURGERY, VASCULAR SURGERY
AND SCIENTIFIC RESEARCH METHODOLOGY**

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PHD THESIS

**PHYSICAL THERAPY-BASED INTERVENTION
FOR REDUCING FOOT ULCER RISK IN PATIENTS
WITH DIABETIC PERIPHERAL NEUROPATHY**

- A B S T R A C T -

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Diabetes-related foot severe complications, the newly introduced concept of "diabetic foot disease" (DFD) (1) and its impact on patients' health and quality of life, patient's families, the medical community and the whole society, were the main elected research themes for this Doctoral Thesis background.

"Physical therapy-based intervention for reducing foot ulcer risk in patients with diabetic peripheral neuropathy", highlights the role of physiotherapists in preventive and curative strategies, on patients at risk to develop diabetes-related foot ulcers (DFUs) and secondary more severe complications as amputations. For this reason, the present research on the assessment protocol and physical therapy-based intervention for patients affected by diabetes-related peripheral neuropathy (DPN), could improve both the approach for reducing foot ulcer risk in "at risk" patients, and the DFU off-loading care. By increasing the awareness on the DFD, the level of physiotherapy profession as part of the multidisciplinary team involved in diabetic foot care, could be raised, and new research in the field could be opened.

International Diabetes Federation (IDF) projections alert a worldwide increase in the prevalence of diabetes mellitus (DM) from 537 million, to 783 million persons until 2045 (2), and Romania showed a crude prevalence of 11.6% since 2014 (3), with numbers continuing to raise. Type 2 DM related complications became the 4th cause of death globally (4). Diabetic peripheral neuropathy, one of diabetes complications affect 23-70% of patients (5) and when peripheral arterial disease (PAD) is associated, can lead to DFD. The risk of developing PAD is 2 to 4-fold higher in people affected by DM (6). Lower limb diabetes-related complications, including DPN and PAD predict ulcers (7), and when all these coexist, disability, hospitalisation and amputation can arise, and global high mortality can further follow diabetes-related lower limb amputations (8).

Late recognition and intervention in DPN and PAD might bring to severe undesired diabetic-related foot complications (9). Diabetic foot ulcer is one such complication affecting 14,8% of diabetic population in Romania (10), with a general lifetime incidence of DFU being between 19-34% (11).

Approximately 50% of people affected by diabetes that present with an ulcer, are affected by PAD, too, which association significantly increases the risk of adverse limb and cardiovascular events (12). After a first ulcer, the risk for re-ulceration increases with up to 40% (13).

In the general population, the prevalence of PAD was found to be 10-26%, while in the population affected by diabetes, the prevalence was found to be between 20-28% (14). In people affected by diabetes, PAD has a special disease pattern, the absence of classical PAD symptoms making the diagnosis of PAD and chronic limb-threatening ischaemia (CLTI) very difficult. Sedentary lifestyle, diabetes neuropathy-related loss of pain sensation (LOPS), are probably the main inhibitor factors for the presence of PAD classical subjective symptoms (15).

Considering the risk of delayed and poor DFU healing and further amputation in presence of PAD, early diagnosis is crucial in people affected by diabetes (14).

Diabetic-related foot ulcers that complicate with amputations, increase therefore the morbidity and mortality rate (16). Up to 85% of non-traumatic amputations in the lower limbs are preceded by DFU, with an annual incidence of DFU being estimated around 2% (11).

When compared to other countries, Romania showed a crude incidence of amputations associated to DM (17). In this people category, after the first major amputation the mortality rate at one year is about 40% (18) and 80% at five years, respectively (19).

Loss of protective sensation (LOPS), is the main risk factor for developing DFU, explaining the re-ulceration high rate (40% within a year and 65% within 3 years) (20). In the presence of PAD and foot deformity, the risk of developing DFU increases even higher (21).

As neuropathy progresses, muscles wasting alters both foot function and joint stability, facilitating the development of foot deformities (22), poor balance and instability, abnormal

plantar pressure (PP) distribution, and when associated with repetitive trauma, more than 50% of foot ulcers can be explained (23). Foot deformities and limited joint mobility (LJM) can present even before the installation of diabetes and its subsequent complications, but can also be a natural diabetic neuropathy consequence (24). There are some evidences that (LJM) around the ankle is present in diabetic population before DPN is diagnosed, as well as some differences have been observed in peak forces of ankle flexors and extensors muscles in both affected and non-affected by DPN populations (25).

Along with neuropathy progression, altered mechanical properties of connective tissues resulted from longstanding hyperglycaemia can contribute to increased passive ankle stiffness and secondary increased stress under the forefoot (26).

In particular, reduced ankle range of motion (ROM) referred as ankle equinus, has been associated with high forefoot PP (27) and related to increased ulcer risk in diabetic population (28).

Early identification of all risk factors (including ankle LJM and reduced foot muscle strength), and early implement of appropriate treatment can change the diabetic foot course.

Recognising ankle limited range of motion (ROM) and all foot deformities and the implication of limited ankle ROM and the muscle strength alterations on abnormal load, requires clinician good skills, training, and technology.

For qualitative analysis of strength, manual muscle testing (MMT) has previously been used to measure muscle strength around the ankle joint (29). As MMT showed low reliability, for more quantitative analyses in relation to foot and ankle muscle strength, hand-held dynamometry, electronic dynamometry and isokinetic testing have been later developed and used. Even though isokinetic testing due to its high reliability, became the gold standard for general muscles strength assessment (30), there is still no widely accepted method for measuring ankle torque or foot and ankle muscle power (31).

In the field of clinical rehabilitation and physiotherapy, when isokinetic testing is not an available assessment tool, electronic dynamometry can become a way to accurately measure foot strength. By dynamometric means, foot and ankle muscle strength can be measured for diagnostics, rehabilitation planning/progression and treatment outcomes monitoring. By capturing ankle torque, indirect muscle strength can be accurately assessed in healthy and affected by conditions participants. Unilateral conditions or bilateral symmetrical conditions affecting gait, such as DPN, might benefit from electronic dynamometry testation. Analysing foot and ankle muscle strength by capturing torque at different ankle angles, could establish some specific muscle parameters during maximal voluntary isometric contraction (MVIC) in both healthy and affected by DM/DPN participants. Finding the weakest ranges could thereafter help in prescribing more specific physical therapy-based exercise programs.

Physiotherapists, as part of the multidisciplinary diabetic foot-care team, with special training and skills, can assess foot and ankle ROM and muscle function by using manual testing and specialized measurement equipment.

This research approaches a new standardised method of the ankle muscles strength assessment to potentially evaluate the relationship between ankle ROM and foot muscle parameters in both healthy and affected by different conditions participants, especially participants affected by diabetic-related neuropathy. A measurement protocol for assessing ankle ROM in relation to muscle strength has been developed during this research. Applied in different participant categories, this protocol could open the path for understanding how ankle ROM impacts on ankle torque in both healthy and affected by DM and DPN participants.

For a reliable and reproducible evaluation of ankle torque in relation to ankle ROM, a measurement device and a measurement method will undergo extensive study in this research. By quantitatively assessing ankle torque with a custom-made portable electronic dynamometer (manufactured for this research), foot and ankle muscles strength in relation to ankle ROM was evaluated.

We hypothesized that with the given custom-made portable electronic dynamometer, accurate ankle torque measurements could be demonstrated and further used for the detection of small changes in the muscle derived signals in DM and DPN participants, with a potential diagnostic role for the DPN specific derived muscle signs in the future.

The relation between plantar pressure and ankle torque/ROM could be thereafter quantitatively assessed and further used to correlate the data in relation to the diabetic foot ulcer risk.

Physiotherapists are also involved in the human physical activity and movement assessment, which became lately of great scientific importance due to the impact that physical activity and physiology of movement have on human health. Sedentary behaviours and their chronic-related complications and how these might influence human health across lifespan, are being studied, with increased sedentary time (ST) being associated with an increased risk for type 2 DM, metabolic syndrome (32) and cardiovascular diseases (CVD) (33), (34).

Studying the concept of physical activity (35), applied to the foot and ankle, became another research main objective. Few studies analysed the impact of sedentary behaviour on the muscles acting around the ankle joint in healthy individuals. Prolonged sitting in people affected by diabetes, revealed a potential negative impact on the foot plantar skin health (36), with few data on the negative potential effect of prolonged sitting on ankle torque.

Our research hypothesis was that a sedentary behaviour could negatively influence foot and ankle muscle strength in healthy participants, with possible negative implications on foot and ankle muscle strength in people affected by DM with/without DPN to be further examined.

Physiotherapists when properly trained, and under medical supervision/prescription, are practitioners able to use medical devices in their clinical practice, including assistive devices, off-loading devices like foot and ankle orthoses (walkers), orthotics, insoles, therapeutical footwear, etc.

With the aim of preventive strategies, the International Working Group on The Diabetic Foot (IWGDF) proposed a screening tool able to include each patient in a risk class considering all factors that can negatively influence the foot in a person with diabetes (37). Beside the IWGDF guidelines on prevention strategies (including ROM preservation), treatment approach and modalities of care for the diabetic foot with an active DFU were published. Considering the chronically delaying pattern of a DFU (38), (39), (40), an algorithm of care for the active ulcers was proposed and this included the use of off-loading devices for the treatment of DFUs and therapeutical footwear for DFU primary and secondary preventive objectives.

Thus, enlarging our research on studies around DFU-care and mainly DFU physiotherapist-assisted treatment in pandemic conditions, we were able to assess the results of our implemented DFU off-loading treatment protocol. We hypothesised that when patients were treated with non-reimbursed off-loading devices for DFU, while being remotely monitored, their buying behaviour would have impacted on the treatment outcomes.

Finally, our research team efforts managed to analyse the data collected from a national data base from 61 hospitals with the aim of calculating the rate of amputations and revascularizations for patients with either cardiovascular or diabetic comorbidities.

To ensure reaching the studies main objectives, our research team brought together professions with multidisciplinary interests, from the medical field (podiatric surgery, vascular surgery, orthopaedic surgery, occupational medicine, physiotherapy, physiology), to biomechanics, statistics, ergonomics, electronics and telecommunications.

The main objectives of this Thesis were to develop a protocol for ankle torque assessment in different populations, situations and conditions, and to evaluate the

effectiveness of physical-therapy-based intervention with off-loading methods applied for DFU home-based treatment under remote monitoring.

Secondary objectives targeted quantitative/objective measurement methods to assess ankle torque in relation to ankle ROM in both healthy participants and affected by acute/chronic conditions, with diabetic-related peripheral neuropathy being of predominant interest.

For the quantitative assessment of ankle torque, a given portable custom-made electronic dynamometer was intended to be studied as a reliable and reproducible method. For the used custom-made device, calibration and measurement method demonstration and ankle torque assessment of various participants and conditions became the research more studied aspects.

This Thesis was organized as independently structured research articles. The main researcher contributions are fully disclosed for each separate published article.

All the studies adhered to the principles outlined in the Declaration of Helsinki – Ethical Principles for Medical Research. All studies were conducted in compliance with the Ethical protocol, the Data Protection Act and other regulatory requirements as appropriate. All studies were initiated after the Ethical protocol was reviewed, and received favourable opinion from the responsible Independent Ethics Committees. All studies (when required) were approved by Ethics Committee of University of Medicine and Pharmacy “Victor Babeș” Timișoara, released and registered under Nr. 50/21.09-14.10.2020.

LIST OF PUBLISHED SCIENTIFIC PAPERS

1. **Drăgoi, I.I.**; Popescu, F.G.; Petrița, T.; Tatu, R.F.; Bondor, C.I.; Tatu, C.; Bowling, F.L.; Reeves, N.D.; Ionac, M. A Custom-Made Lower Limb Dynamometer for Assessing Ankle Joint Torque in Humans: Calibration and Measurement Procedures. *Sensors* **2022**, 22, 135. <https://doi.org/10.3390/s22010135>; IF=3,9
2. **Dragoi, I.I.**; Popescu, F.G.; Petrita, T.; Alexa, F.; Tatu, R.F.; Bondor, C.I.; Tatu, C.; Bowling, F.L.; Reeves, N.D.; Ionac, M. A Custom-Made Electronic Dynamometer for Evaluation of Peak Ankle Torque after COVID-19. *Sensors* **2022**, 22, 2073. <https://doi.org/10.3390/s22052073>; IF=3,9
3. **Dragoi, I.I.**; Popescu FG, Petrita T, Alexa F, Barac S, Bondor CI, Pauncu EA, Bowling FL, Reeves ND, Ionac M. Acute Effects of Sedentary Behavior on Ankle Torque Assessed with a Custom-Made Electronic Dynamometer. *J Clin Med.* **2022**, Apr 28;11(9):2474. doi: 10.3390/jcm11092474. PMID: 35566600; PMCID: PMC910560; IF=3,9
4. **Dragoi, I.I.**; Petrita, T.; Popescu, F.G.; Alexa, F.; Barac, S.; Bowling, F.L.; Reeves, N.D.; Bondor, C.I.; Ionac, M. A Signal Processing Method for Assessing Ankle Torque with a Custom-Made Electronic Dynamometer in Participants Affected by Diabetic Peripheral Neuropathy. *Sensors* **2022**, 22, 6310. <https://doi.org/10.3390/s22166310>; IF=3,
5. **Dragoi, I.I.**; Popescu, F.G.; Bowling, F.L.; Bondor, C.I.; Ionac, M. Patients' Buying Behavior for Non-Reimbursed Off-Loading Devices Used in Diabetic Foot Ulcer Treatment—An Observational Study during COVID-19 Pandemic from a Romanian Physical Therapy Unit. *J. Clin. Med.* **2023**, 12, 6516. <https://doi.org/10.3390/jcm12206516>; IF=3,9
6. Ionac, S.; Rogers, S.K.; Bondor, C.I.; Bowling, F.L.; **Dragoi, I.I.**; Ionac, M. Lower Extremity Amputation and Peripheral Revascularization Rates in Romania and Their Relationship with Comorbidities and Vascular Care. *J. Clin. Med.* **2024**, 13, 52. <https://doi.org/10.3390/jcm13010052>; IF=3,9

Multiple studies that addressed the calibration and validation of a new custom-made electronic dynamometer used for ankle torque measurements were planned. Evaluation of the reliability and reproducibility of the used measurement device was conducted in different studies, on different populations, in different conditions, including healthy participants and affected by acute and chronic conditions, with a main focus on foot muscle-derived signals in individuals affected by DM and DM with DPN.

Another observational study conducted for this Thesis remotely analysed the impact of an off-loading approach protocol for DFU treatment, while the last study calculated the Romanian rates of amputations and revascularizations for patients with either cardiovascular or diabetic comorbidities from a national data base from 61 hospitals.

Firstly, diabetic foot concept was described in relation to its associated risk factors. Main mechanical and non-mechanical risk factors were reminded, with ankle ROM and ankle torque being the primary aspects that conducted to the main research methods.

Ankle torque assessed with a custom-made electronic dynamometer during MVIC, was the main measurement method used. The proposed quantitative assessments for the ankle torque measurements imposed that the methods used were previously tested, the apparatus was first calibrated and a measurement procedure then elaborated, ensuring thereafter the accuracy of the resulted data.

The Thesis was mainly concentrated on the innovative method for ankle torque measurement using a portable custom-made electronic dynamometer and the studies around calibration and measurement protocol. While measuring healthy participants, with the resulted data, the calibration and measurement procedure for the custom-made electronic dynamometer were elaborated.

During measurements some participants were diagnosed positive to SARS-CoV-2, this further allowing to assess the impact of this particular acute condition on ankle torque when compared to non-affected individuals. Reliability and reproducibility for the used dynamometric measurement method was demonstrated.

A third study, demonstrated that the same used dynamometric measurement protocol was a very good method to assess ankle torque in time in both sedentary and active life-style participants that were supposed to short term active and sedentary behaviours.

A fourth study analysed in detail the whole signal processing method used when ankle torque was assessed using the given portable custom-made electronic dynamometer. During the validation of measurement procedure, patterns of muscle efforts-derived signals were recognised and presented as possible detected DPN-related type of signals.

A fifth study was conducted as an observational prospective cohort study. The monitorization of patients was performed through a free smart-app, using self-captured foot photography. The study reached to analyse the patients' buying behaviour for non-reimbursed off-loading devices used to treat DFU, while being remotely monitored. The results showed that buying behaviour was dependent on the medical condition severity and some personal factors. Male sex, rural origin and poor financial status negatively influenced patients' buying behaviour for removable cast walkers (RCWs). All afferent costs for the used off-loading approach and all the encountered situations during remote monitoring were fully disclosed.

The last study retrospectively analysed 61 Romanian hospital-based database for 2019, covering 44.9% of the amputations for that year, and used the national database to follow amputations and revascularizations between 2016 and 2021. To calculate the rates of amputations and revascularizations for patients with either cardiovascular or diabetic comorbidities and further detail a comparison between rates, was this study main aim.

The first four studies obtained results, opened the path for custom-made electronic dynamometry as a method for ankle torque assessment in both healthy and affected by acute and chronic conditions including DPN participants.

The data resulted from the fifth study are of great importance since we managed to report the DFU treatment outcomes and the arisen complications while patients with diabetic-related foot ulcers were remotely monitored.

The results from the sixth study indicated that Romanian patients have a high risk of amputation, probably 6 years earlier than Western European countries. A high number of cases over the age of 40 (77%) had both PAD and diabetes (43.8%), with PAD showing to be the most prevalent comorbidity for amputation in Romania.

General scientific objectives of this Thesis were to develop a “Protocol” for assessment and intervention with physical therapy-based methods for reducing foot ulcer risk in patients with diabetic peripheral neuropathy. Describing the assessment devices used for ankle torque captures, including the calibration protocol for the apparatus used for measurements (Study 1), assessing the reliability and reproducibility for the used custom-made device (Study 2), assessing the reproducibility in time and analysing the impact of active and sedentary behaviour on ankle torque assessed with the used electronic dynamometer (Study 3), were the main general scientific objectives of our first three studies.

To present the signal-processing chain and data processing used for dynamometric ankle torque evaluation in healthy participants and affected by DPN, was the general objective of the 4th Study, while to expose the patients’ buying behaviour for non-reimbursed off-loading devices proposed for DFU treatment during COVID-19 pandemic, were the 5th Study main general objectives. The last study (Study 6), main general aim was to conduct a retrospective Romanian nationwide data analysis on the number of revascularization and amputation procedures in patients with vascular and diabetic comorbidities.

The first Study specific scientific objectives were to fully disclose the measurement procedure for ankle torque evaluation while establishing the method reliability.

The specific aim of the second Study was to assess the impact of COVID-19 on foot muscle strength while evaluating the reproducibility of peak ankle torque measurements in time measured with the given custom-made electronic dynamometer.

Study 3 aimed to specifically analyse the impact of a short-time sedentary versus a short-time active behaviour and to compare the effects on the evolution of peak ankle torque in time. Another specific scientific objective was to assess the impact of sedentary and active lifestyle types on ankle torque when participants were subjected to a short-time active/sedentary behaviour.

Study 4 specifically aimed to disclose all the encountered situations, possible errors and the validation of measurements, and to present resulted time-graphs that possibly captured DPN-specific derived-signals.

The main specific scientific objective of the 5th Study was to analyse how patients’ buying behaviour for non-reimbursed off-loading devices influenced the DFU treatment outcomes during a remotely assisted treatment in COVID-19 pandemic times.

Study 6 main specific scientific aim was to evaluate the number and type of amputations performed in Romania between 2016 and 2021 and establish the most common vascular and diabetic comorbidities associated, based on the data collected from a nation data-base.

Conclusions and personal contributions

In March 2020 the COVID-19 pandemic situation imposed the lock-down period and safety measurements. Population at risk was instructed to avoid social contact and have only emergencies as reasons for social exposure. For this reason, we considered unethical to expose participants at contagious risks for the whole lock-down and emergency/alert period, and the cessation of participant recruitment followed for both healthy and affected by DM/DPN individuals. With the already collected data we have managed to elaborate four research articles. With the participants data resulted after initial visit in the Physiotherapy Unit, we managed to elaborate the 5th article. Participants treatment was remotely monitored, ensuring thereafter safety measures for all patients enrolled in this 5th observational prospective study.

The first four articles mainly addressed the calibration, validation of the used electronic custom-made dynamometer, the fully disclosure of measurement protocol for assessing ankle torque in both healthy and affected by pathologies participants, and the complete data processing algorithm description for the measurement obtained data from healthy individuals and participants affected by DM with DPN.

The fifth article managed to expose the factors that influenced patients buying behaviour for non-reimbursed off-loading devices used for DFU treatment during COVID-19 Pandemic.

The sixth research article managed to analyse the current rate and number of revascularization and amputation procedures, with vascular and diabetic comorbidities, as well as the vascular care that Romanian patients received between 2016-2021, with a major interest during COVID-19 pandemic.

We have reached the main aims of our studies and mentioned limitations, unreachd points and addressed future research perspectives.

Conclusions from Study 1

Our portable electronic custom-made dynamometer showed to be a reliable clinical measurement tool for ankle torque evaluation, enhancing thereafter the method diagnostic accuracy, and the future implication of the device int the treatment monitoring and the outcomes evaluation. Such devices could be beneficial for establishing new normative data for foot and ankle strength parameters in healthy and affected by conditions populations. Due to its manoeuvrability and low costs portable dynamometers could open the possibilities for on-site clinical and experimental foot strength testing.

Conclusions from Study 2

In our study, the mild form of COVID-19 had no impact on ankle peak torque. We can comment on our results as being related to the small sample size. By considering the same study design with a bigger sample size, future studies could evaluate test–retest reproducibility with better precision. The reduced probability in our group to develop COVID-19 while participating in another longitudinal study was considered a situation by chance, limiting thereafter our sample size.

As peak torque variability was similar in both groups, and peak torque during MVIC demonstrated no significant statistical differences between groups, we believe that other muscle parameters, such as endurance, force steadiness and force variation during repetitive MVIC, could be evaluated to better assess the possible implication of COVID-19 on foot muscle parameters. New insights in motor control levels could be opened if MVIC would be analysed as a functional task, and not as a single maximal volitional effort.

In case of repetitive ankle peak torque in dynamic assessment, we managed to demonstrate the reproducibility of our portable custom-made electronic dynamometer.

A bigger sample size with individual measurements repetitively recorded in two or more occasions in the same conditions could be considered for future research.

Conclusions from Study 3

The more time participants maintained either short-term static or short-term active behaviour, the lower the average peak ankle torque resulted in both situations. While both routinely active and routinely sedentary participants showed a decrement of force in time when maintaining both types of behaviours, sitting position was associated with a lower value of average peak ankle torque during maximal voluntary isometric contraction.

Future studies should establish whether a threshold for the time spent in a sitting position/ sedentary behaviour would be beneficial in relation to foot muscle strength. Analysing whether breaking the routine during a specific activity might positively change the muscle force results.

Our force measurement results could complete ergonomic improvements with the aim to achieve healthy foot status in individuals spending prolonged time in a sitting position.

Repeating the experiment in other types of groups of participants and possibly in groups affected by different pathologic conditions, and especially on participants affected by DM with DPN, could be considered for future studies.

Conclusions from Study 4

A better understanding of dynamometrical captured muscle efforts-derived signals is needed, especially when the measurement data is collected from both healthy individuals and individuals affected by conditions. When portable custom-made electronic dynamometry is used for ankle torque measurement in participants affected by DPN, signal processing is required. The signal characteristics collected from the time graphs should be carefully interpreted when a medical perspective is the main aim.

As not all distorted oscillograms are errors, the captures appearing as possible errors need comprehensive analysis when the measurements are related to chronic conditions as DPN. In the presence of DPN, distorted signal detected by time graphs interpretation, may represent the natural aspect of the signal in presence of the pathology.

Analysing foot and ankle muscle strength through ankle torque dynamometry is essential in the presence of DPN, and quantitative resulted data could offer more precise information for the risk analysis and personalized physical-therapy based treatment.

Future research should consider the analysis of the differences obtained on the time graphs between healthy and affected-by-DPN participants, which could further be used in the process of screening and pathology detection.

Analysing in detail the differences between spectral components belonging to healthy and affected-by-DPN participants could open new perspectives in DPN diagnostics. Specimens of discarded measurements could be useful as reference for future studies and trials.

New research should consider the false automatically detected errors as possible first signs of DPN in the early stage of the condition.

A precise working algorithm used alongside with electronic custom-made dynamometry, can become a valuable tool for ankle torque measurement, rehabilitation pathways development, progression and treatment outcomes monitoring in participants affected by DPN.

Conclusions from Study 5

Patients' buying behaviour for the given off-loading devices was dependent on the medical condition severity and personal factors.

A more severe condition (HBP, PAD, increased number of past amputations) determined whether patients bought RCW instead of therapeutic footwear. Male sex, rural origin and poor financial status negatively influenced patients' buying behaviour for RCWs.

During the COVID-19 pandemic, patients with a DFU addressed with delay for off-loading treatment.

Remote monitoring supervised by trained health care practitioners could become a method for self-independent patients with DFUs treated with removable devices.

However, remote DFU treatment needs precautions due to possible situations that could alter the outcomes (poor hygiene, errors in bandage utilization, reduced technical capacity, lack of needed consumables/skills, and inability to properly self-care, especially when living alone, etc.).

Some recommendations that derived from the study, addressed the need for improving the quality of home-self-based treatment when foot captures are being used to remotely monitor DFUs off-loading treatment with removable non-reimbursed devices.

In the same manner, the deterioration of the removable devices (RCWs, footwear, insoles), imposes the necessity to closely monitor the prescribed off-loading used devices status in order to prevent adverse events or poor treatment quality.

Conclusions from Study 6

Our research resulted data indicated that Romanian patients probably have a high risk of amputation, approximately 6 years earlier than some Western European countries. For a true comparison to be allowed, international data need age-standardization. Over the age of 40 in Romania (77%), where a high number of cases had both PAD and diabetes (43.8%), PAD showed to be the most prevalent comorbidity for amputation. By implementing a vascular surgeon's clinical investigation before lower extremity amputation, in Romania, the number of amputations could be reduced. The high number of amputations completed by general surgeons in Romania impose awareness raising between patients and physicians, about the importance of revascularization decisions and the vascular surgical input. A vascular registry that collects data from all European countries, led by the European Society of Vascular Surgery, would contribute in marking the trends and disclose the international disparity.

Personal contributions

Personal contributions mainly addressed clinical, and research implications. During the first four studies, the clinical contribution involved personal participation in the Physiotherapy Unit, where participants were consecutively interviewed, anamnestic data (personal, anthropometric, demographic, lifestyle, comorbidities, smoking status, physical activity) were collected, and measurements (clinical tests, functional tests and force dynamometrical captures) were performed for all consenting participants. All participants enrolled in the studies consented for participation and data (including photos) usage and data publication.

For all participants that underwent a foot exam, ROM, presence of deformities, reported daily steps were registered. All measurements were supervised, dynamometrical data registered, adverse reactions noted, and the standardized measurement protocol closely respected. The main researcher ensured permanent functionality of all the measurement equipment used and complete disponibility for assessments, measurements and phone-call

assistance or any form of virtual assistance for all studies participants in case needed during the whole research period.

The research activity mainly consisted of rigorous documentation of the scientific literature with the focus on current status of DFD, the relation between DM, DPN, PAD and mechanical risk factors for DFU. A special attention was given to the relation between reduced ankle ROM and the risk of ulceration in the forefoot, the equipment lately used for foot strength assessment and the role physiotherapists have in the multidisciplinary team around diabetic foot care. Preparation of the documentation used for the Protocol elaboration was also performed.

In order to possibly perform all required measurements, procedures for the acquisition of all measurement devices were implemented. Main acquisitions were self-sponsored.

Recruitment at the Physiotherapy Unit was consecutively performed for all the consenting participants for the dynamometric measurements in the first Study and the selection of participants, respectively for the interventional study (Study 3). All dynamometrical measurements resulted data from participants, including participants affected by acute conditions as SARS-CoV-2 infection, were collected for the second Study for further analysis and process of ankle torque derived signals. Participants in the second study were selected "by chance". All data derived from all measurements from all initial three studies, were collected for resulted signal process and analysis for the fourth study.

An electronic data base was created for participants data registration as per statistician requests, strict contact with the supervisors and whole research team was maintained, and all their comments considered.

The articles format was conceptualized, scientific journals for publishing was elected and writing ensured journal requests. After the extensive reviewing sessions, an acceptance certificate for publication was received and all four articles published. As the research methodology, full description of the calibration and measurement method were fully disclosed, as well as the data processing, signal analysis, and all errors reported, our research is reproducible, excepting the specific "de novo" conditions met for the COVID-19 group.

For the fifth Study, the main researcher clinically contributed at the participants first visit for interviewing, data registration, consent sign and foot exam (ROM, presence of deformities, DFU marking), verbal and written education on foot-care. After a complete foot exam, the off-loading devices were selected based on patients' needs and acceptance and DFU imprinting was performed before the off-loading device application. Virtual assistance and monitoring were ensured for the whole study period, constant on-site presence was ensured if needed, and availability for consumables and off-loading devices was guaranteed.

A rigorous literature research was planned, followed and considered for the best practice of off-loading, while still considering the available methods. Patients' recruitment was followed by data registration according to the statistician needs. Constant contact was maintained with the medical foot-care team and the research supervisors. The scientific article conceptualization, writing and editing followed after the appropriate scientific journal was selected. After an extensive reviewing session, the article received favourable answer for publication.

As a member of "CerVasc", Research Centre for Vascular and Endovascular Surgery, Medical School, University of Medicine and Pharmacy „Victor Babeş", Timișoara, and part of the team involved in the elaboration of the sixth Study, between 2022-2023, the main personal contribution was around the documentation in the scientific literature, validation and visualization of the resulted material prepared for publication. Considering the negative impact PAD has on the foot of patients affected by DM and DPN and the high risk for DFU, the sixth study completes the Doctoral Thesis research theme bringing important data on the number and type of amputations in Romania between 2016-2021.

We hope that all these scientific contributions will improve the knowledge on ankle dynamometry in relation to diabetic foot, and participate in the early diagnosis of DPN, reduction in amputation numbers, improvement of patient's well-being and quality of life, professional work status and further reduce disability, mortality and health system costs. This physical-therapy approach could contribute in raising the level of physiotherapy profession in the multidisciplinary team involved in the diabetic foot care.