Conceptual multimodal optical approach for diagnosis of foot ulcers in diabetic patients

D. SAVASTRU[a], S. MICLOS[a], S. DONTU[a], G. INCEU[b,c], C. BONDOR[b,c],
[a]*National Institute of R&D for Optoelectronics - INOE 2000, 409 Atomistilor St., Magurele, Ilfov, RO-077125, Romania*
[b]*"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj, RO-400012, Romania*
[c]*Medical Center for Podiatry, 10 Iuliu Moldovan St., Cluj-Napoca, Cluj, RO-400348, Romania*

A novel technology for diagnosing foot ulcers is being proposed. There exists an urgent need for a clinical tool capable of probing multiple markers involved in foot ulcer formation and development, such as oxygen perfusion, blood flow, and vascular structure, at both epithelial and muscle layers of the foot. Currently, there are no single modality instruments capable of performing comprehensive measurements at the both muscle and epithelium to predict ulcer formation. To address this issue, we envision the use of combined near-infrared spectroscopy (NIRS) and Optical Coherence Tomography (OCT) within the same instrument with the goal of deriving complementary information related to foot ulcer formation and therapy progression. The combination of these two techniques will provide a unique marker that may enable early prediction and monitoring of diabetic foot ulcers.

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1. Introduction

Diabetic foot disorders represent a major cause of morbidity and mortality in patients with diabetes [1] and are associated with a high rate of hospitalisation and resource utilisation [2]. The term "Diabetic foot" defines a broad range of disorders of the feet in patients with diabetes (such as diabetic neuropathy, peripheral vascular disease, Charcot's neuroarthropathy, foot ulceration, osteomyelitis) that can lead to tissue destructions which may finally impose performing of lower limbs amputations [3]. The risk of developing a foot ulcer during lifetime in a person with diabetes may be between 15% and 25% [4] and foot ulcers are considered the leading precursor to lower extremity amputations in patients with diabetes. There is strong evidence that patients with diabetic foot ulcerations have a higher risk of all-cause mortality compared with patients with diabetes but without a history of foot ulcerations [5]. It is estimated that more than a million people with diabetes require limb amputation each year, suggesting that one major amputation is performed worldwide every 30 seconds [6]. Some population-based studies reported a 0.5% to 3% annual cumulative incidence of diabetic foot ulcers [7,8,9]. The incidence of new foot ulcers was determined in a large cohort of diabetic subjects, as a part of the Northwest of England diabetes foot care study, and the reported annual incidence rate of new diabetic foot ulcerations was 2.2% [10]. According to one large British study of neuropathic patients, the 1-year incidence of initial foot ulcer was 7% [11]. The prevalence of foot ulcers reported in epidemiological studies ranges from 2% to 10% [7,11,12]. Foot ulcers are considered to be the precursor to approximately 85% of lower limb amputations in persons with diabetes, and 7% to 20% of patients with foot ulcers will require an amputation [13,14,15]. A study carried out by the European study group on diabetes and the lower extremity (Eurodiale) reported that 5% of diabetic patients with a foot ulcer required major amputation during the 12-month follow-up period [16]. Diabetes proved to be the most common underlying cause of nontraumatic lower extremity amputations in the US and Europe [17,18]. Amputation induces a significantly elevated mortality, ranging from 13% to 40% at 1 year to 39–80% at 5 years [4]. Survival rates after amputation are lower for diabetic versus nondiabetic patients [19]. It is considered that in the next two years after a major amputation, 50% of patients will undergo an amputation on the other foot and 5-year mortality rate after a limb amputation is 68% [20]. A Sweden study reported a 5-year mortality rate of 68% after lower limb amputation, with survival rates lower among patients who underwent higher levels of amputation [19].
The results of a study conducted in Romania between 2006-2010, who aimed to performed a national evaluation of the frequency, incidence and trends of diabetes-related lower extremities amputations, showed that, during the five years of the study, there was an increase in the absolute number of major amputation (above the ankle), as well as of minor amputations [21]. The findings of a post hoc analysis of quality of life for diabetic neuropathy

(QOL-DN) patients in a cross-sectional survey performed in 2012 in Romania, using the Norfolk QOL-DN in which 21,756 patients with self-reported diabetes were enrolled, showed that of the 21,174 patients included in the analysis, 14.85% reported a history of foot ulcers and 3.60% reported an amputation. The highest number of amputations was reported in the 70–79-year age group (largest group). Compared to patients without foot ulcers, those with foot ulcers had significantly higher scores for total QOL-DN and all its subdomains translating to worse quality of life [22,23]. Although amputation rates for people with diabetes have decreased in the past decade, they remain exceedingly high compared to nondiabetic populations [24,25]. It is essential, therefore, that every effort possible is made to prevent foot problems, and if they do occur, to be aggressively and early manage. The complications of diabetic foot remain a public health problem worldwide, although it is widely recognized that this problem is not an insurmountable one and that most amputations are preventable and most ulcers can be treated and cured with a proper management and a well-organized health care system.

Diabetic foot ulcers have a multifactorial nature [26,27], being considered that the most important risk factors involved in pathophysiology of diabetic foot are peripheral neuropathy, vascular disease, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity [1,28,29]. Of these, the most frequent factors that interact and ultimately cause ulcers in people with diabetes, are neuropathy, deformities and trauma. Recognition of these risk factors and appropriate treatment of diabetic foot requires a skilled ability to diagnose, manage, treat and proper educate the person with diabetes [30]. Integrating clinical knowledge and experience through a multidisciplinary approach that promotes a more efficient management, finally contributes to reducing the risk of amputations.

Diabetic neuropathy may be present in more than half of diabetic patients over 60 years and increases the risk of foot ulceration by 7-fold [31,32]. Diabetic neuropathy can affect the sensory, motor and autonomic nervous system components to varying degrees, but peripheral sensory neuropathy is the primary factor leading to diabetic foot ulcerations [28]. It is considered that 45% to 60% of all diabetic ulcers are purely neuropathic, while up to 45% have neuropathic and ischemic components [13]. Motor and autonomic neuropathy also plays an important role in foot ulcerations.

The relationship between diabetes mellitus and peripheral artery disease is a complex one, diabetes being considered a major risk factor for peripheral artery disease. The prevalence of the vascular disorder can vary between 10% and 40% in diabetic people [33] and the mortality rate in diabetic patients with peripheral artery disease who suffered an amputation is 50% at 2 years [34]. The incidence of peripheral artery disease among people with diabetes increased significantlly in the last two decades, so the percentage of patients with ischemic or neuro-ischemic ulcers increased compared with that of patients with neuropatic ulcers [35]. Peripheral artery disease in the presence of a foot ulceration, leads to prolonged healing, causing an elevated risk of amputation, and therefore, early recognition and aggressive treatment of lower extremity ischemia are vital to lower limb salvage.

The management of diabetic foot cases is best accomplished by combining the control of glycaemia, infection, offloading of high-pressure areas, vascular status of lower extremities and local wound care. Diabetic foot ulcers and amputations represents a major burden not only for the patient and his family but also for the health care systems, so all the efforts should be directed toward restoring and maintaining an ulcer-free lower extremity with functional limb salvage as the ultimate goal.

The proposed study is motivated by the heavy physical and economic toll exacted by diabetic foot ulcers, which has been estimated to singlehandedly comprise up to 1% of total health care costs in the developed world [36]. Currently, the diagnosis of foot ulcers relies heavily on subjective tests (e.g., wound measurement, tissue colour, palpation) and requires significant clinical experience. Therefore, the diagnosis can vary widely among practitioners [37]. Thus, there exists a need for a clinical technology capable of probing multiple markers involved in ulcer formation and development, such as oxygen perfusion, blood flow, and vascular structure, at both epithelial and muscle layers of the foot.

Unfortunately, current single modality instruments performing tissue measurements do not examine both muscle and epithelium, and thus cannot provide a comprehensive profile of ulcers. To address this issue, we propose to combine near-infrared spectroscopy (NIRS) and Optical Coherence Tomography (OCT) within the same instrument with the goal of deriving complementary information related to foot ulcer formation and therapy progression. The combination of these two techniques will provide a unique measurement tool that will enable early prediction and monitoring of diabetic foot ulcers. NIRS allows for deep tissue assessment of blood oxygenation and tissue perfusion, while OCT enables the examination of surface tissue blood flow and vasculature. Benefits of the proposed approach include: (1) Quantitative, direct, and spatially defined tissue measurements; (2) Correlation and co-registration of deep tissue (muscle) and superficial (skin) measurements; (3) Microvascular-scale imaging of vasculature and blood flow, and (4) Non-contact configuration that avoids wound insult. All these capabilities will allow clinicians to perform comprehensive measurements to predict ulcer emergence and monitor ulcer progression toward healing or chronic endpoints. The specific aim of this proposed study is to develop a noncontact NIRS/OCT instrument capable of co-registering deep and superficial indicators of ulceration. These two complementary techniques are combined within a noncontact imaging probe, co-registering measurements on the same graphics user interface, and providing clinicians with complimentary measurements that will facilitate measurement of disease markers.

2. Potential approach

2.1. Instrumentation

A dual modality NIRS/OCT instrument is being proposed. The concept of this instrument is shown in Fig. 1, while the two main subsystems, NIRS and OCT are detailed in Figs. 2 and 3. The NIRS subsystem (Fig. 2) uses a laser unit consisting of two laser diodes (690 nm and 835 nm) that emit short pulses (a few hundred of ps) with a frequency of 20 to 80 MHz. A PDL 800 laser controller (Pico Quant) is used to power up the laser diode modules. The same controller also sends a trigger synchronization pulse to the photon counting board (Model SPC 130, Boston Electronics). The laser diodes are time-multiplexed so that there is no overlap of successive 690 nm and 830 nm light pulses. This is made possible by using coaxial cable delay lines, as shown in Fig. 2. A wavelength-division multiplexer (WDM) is used to combine the two wavelengths within the same optical fibre. A fibre optic switch (DiCon, USA) is then used to distribute the light to several optical paths (for simplification, only 4 are shown in Fig. 2). The beams exiting the NIRS subsystem are collimated by fibre-coupled collimators, denoted as NC in Fig. 1 and sent to the sample surface via a dichroic mirror and a scan lens (0.11 NA objective), which will focus light onto the skin. Diffuse light exiting the foot is collected by the same scan lens and reflected by the dichroic mirror towards NIRS subsystem. A filter wheel is used to sequentially send light to detectors, such that the detector corresponding to the same spatial location to the illuminating beam is blocked, while the others are collecting light. The output of the PMT (photomultiplier tube) is preamplified by a HFAM-26 module (Boston Electronics) before being routed by an HRT-81 module (Boston Electronics) to a photon counting board SPC 130 (Boston Electronics), which is mounted into a PC. The detection gate is synchronized with the laser sources, so that the arrival of sequential pulses from each wavelength source will be discriminated. The fibre optic switch illuminates the tissue via each collimator sequentially to define the measured region and create a four-quadrant spatial map.

The OCT subsystem is shown in Fig. 3. This system is based on the swept source approach and uses a standard fibre optic-based interferometric system (10/90 fibre coupler). The light from the light source (λ = 1300 nm and $\Delta\lambda$ = 125 nm) is split into the sample and reference arms of the interferometer. The fringe signals are digitized and processed by a custom real-time signal processing board, which is described in detail elsewhere [38-42]. The theoretical axial resolution of the OCT subsystem (Δz = 0.44 $\lambda^2/\Delta\lambda$) is about 6 μm for a source with a central wavelength λ of 1300 nm and a bandwidth $\Delta\lambda$ of 125 nm, and the theoretical lateral resolution (Δx = 0.46 λ/NA) is about 5.5 μm for NA = 0.11.

A LabVIEW software interface can be used to control acquisition and processing data for both subsystems. It will enable the setting of the imaging parameters for each subsystem, as well as for data display and saving.

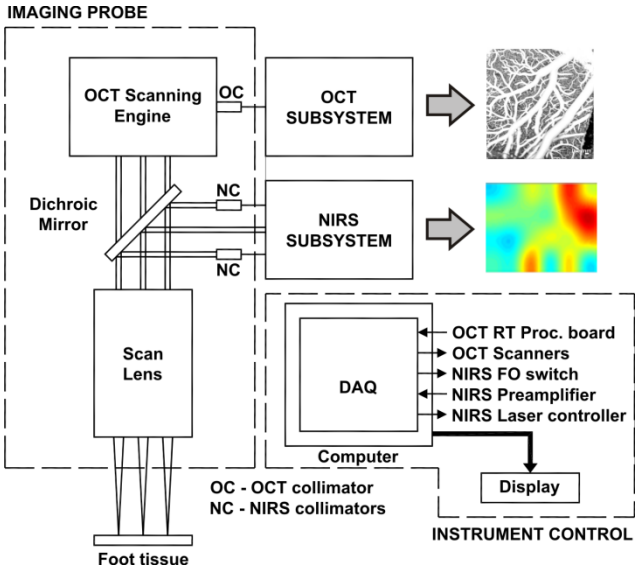

Fig. 1. The concept of combined NIRS/OCT for foot ulcer diagnosis

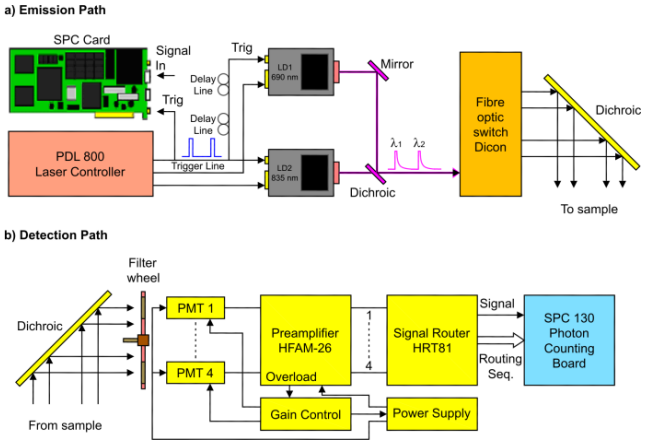

Fig. 2. Schematic representation of NIRS subsystem

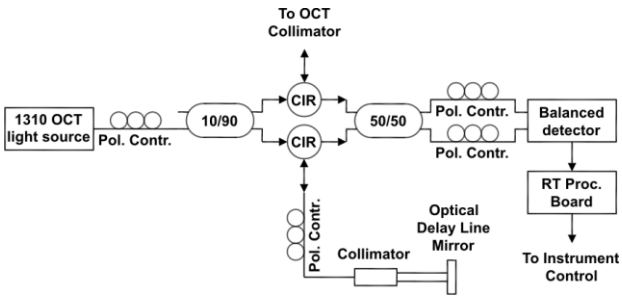

Fig. 3. Scheme of OCT subsystem

2.2. Expected benefits of combined NIRS-OCT imaging

Current diagnosis of the hematologic and vascular health of diabetic limbs rely heavily on subjective tests and therefore in a large disagreement between clinicians. To address this issue, our proposed technology will enable the use of specific metrics for foot ulcer evaluation, such as deep tissue oxygenation and superficial tissue perfusion, as well as modifications in the vascular network. These measurements will be enabled by the concurrent use of near-infrared spectroscopy (NIRS) and optical coherence tomography (OCT). NIRS measurements have been shown to predict ulcer healing outcomes weeks before becoming clinically apparent [43-45].

Oxygenation measurements, similar to cuff occlusion measurements performed by other groups (see Fig. 4) [46], will show if the deep tissue has oxygen deprivation or not. While NIRS is an exciting deep tissue imaging modality that can predict the formation of deep ulcers, studies utilizing NIRS have not demonstrated capability of detecting superficial ulcers [47]. Therefore, we propose to add the OCT capability to our instrument. OCT will allow us to visualize changes in blood flow and vascular morphology that precede the onset of visible damage and follow treatment. We envision that skin angiography measurements with OCT (see an example in Fig. 5), may be used to predict the emergence of tissue damage before it is visible to the naked eye [48]. In addition, NIRS and OCT can be used to evaluate the effects of peripheral vascular disease (PVD) on blood flow on the affected muscles and skin. Given that the diagnosis of PVD is currently based on the blood flow in large vessels, identifying its effects on the end organs (muscle and skin) can be an important aid to the clinician in deciding when to intervene and follow-up the efficacy of a chosen intervention.

Based on these hypotheses, we expect that this multimodal optical approach will be capable of probing multiple markers involved in ulcer formation and development, such as oxygen perfusion, blood flow and vascular structure, at both epithelial and muscle layers of the foot.

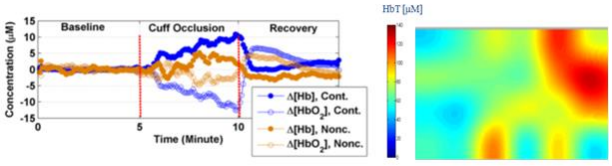

Fig. 4. Oxygenation measurements during cuff occlusion. Blue (orange) curves are measurements by contact (noncontact) probe. Tissue perfusion maps can be obtained as well (see right side image). Image courtesy of N. Iftimia, Physical Sciences Inc., USA

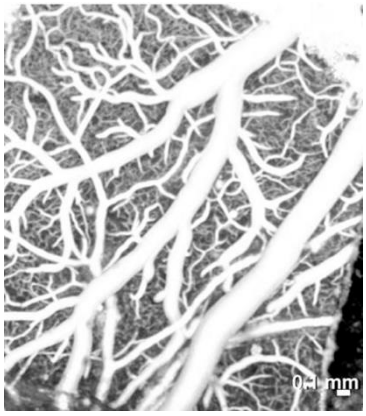

Fig. 5. Wide-field OCT angiography [49]

3. Proposed approach for real-time data analysis

The onsite evaluation of ulcer formation requires real-time processing of the NIRS-OCT data. Due to the multitude of data processing steps, regular PC computation will take longer time than needed. Therefore, we propose a graphical processing architecture. We already took preliminary steps and put together a graphics processing unit (GPU) - embedded software for real-time OCT data processing. Our next step will be to add the NIRS processing. Since the NIRS data processing uses simpler math than OCT, we do not envision any major difficulty in completing this new step. As observed, the easily to comprehend NIRS/OCT maps will enable clinician to make a more informed diagnosis.

4. Conclusions

In conclusion, the combined NIRS-OCT approach proposed in this paper has the goal to improve diabetic foot ulcer diagnosis.

OCT subsystem will allow us to visualize changes in blood flow and vascular morphology that precede the onset of visible damage and follow treatment, which is very important to determine early changes in tissue morphology and functionality that are indicators of ulcer formation.

Complementary, NIRS imaging can predict the formation of deep ulcers and evaluate the effects of peripheral vascular disease on blood flow on the affected muscles and skin.

Thus such an instrument can be an important aid to the clinician in deciding when and how is best to intervene.

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References

[1] R. G. Frykberg, Am. Fam. Physician **66**, 1655 (2002).
[2] M. Kerr, G. Rayman, W. J. Jeffcoate, Diabet. Med. **31**, 1498 (2014).
[3] M. P. Khanolkar, S. C. Bain, J. W. Stephens, QJM **101**, 685 (2008).
[4] N. Singh, D. G. Armstrong, B. A. Lipsky, JAMA **293**, 217 (2005).
[5] J. R. W. Brownrigg, J. Davey, P. J. Holt, W. A. Davis, M. M. Thompson, K. K. Ray, R. J. Hinchliffe, Diabetologia, **55**, 2906 (2012).
[6] W. Jeffcoate, K. Bakker, Lancet (London, England) **365**, 1527 (2003).
[7] S. E. Moss, R. Klein, B. E. Klein, Arch. Intern. Med. **152**, 610 (1992).
[8] S. D. Ramsey, K. Newton, D. Blough, D. K. McCulloch, N. Sandhu, G. E. Reiber, E. H. Wagner, Diabetes Care **22**, 382 (1999).
[9] S. Kumar, H. A. Ashe, L. N. Parnell, D. J. Fernando, C. Tsigos, R. J. Young, J. D. Ward, A. J. Boulton, Diabet. Med. **11**, 480 (1994).
[10] C. A. Abbott, A. L. Carrington, H. Ashe, S. Bath, L. C. Every, J. Griffiths, A. W. Hann, A. Hussein, N. Jackson, K. E. Johnson, C. H. Ryder, R. Torkington, E. R. Van Ross, A. M. Whalley, P. Widdows, S. Williamson, A.J. Boulton, Diabet. Med. **19**, 377 (2002).
[11] C. A. Abbott, L. Vileikyte, S. Williamson, A. L. Carrington, A. J. Boulton, Diabetes Care **21**, 1071 (1998).
[12] D. P. Walters, W. Gatling, M. A. Mullee, R. D. Hill, Diabet. Med. **9**, 354 (1992).
[13] R. G. Frykberg, T. Zgonis, D. G. Armstrong, V. R. Driver, J. M. Giurini, S. R. Kravitz, A. S. Landsman, L. A. Lavery, J. C. Moore, J. M. Schuberth, D. K. Wukich, C. Andersen, J. V. Vanore, J. Foot Ankle Surg. **45**, 66 (2005).
[14] D. J. Margolis, L. Allen-Taylor, O. Hoffstad, J. A. Berlin, Wound Repair Regen. **13**, 230 (2005).
[15] "Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. American Diabetes Association", Diabetes Care, **22**, 1354 (1999).
[16] L. Prompers, N. Schaper, J. Apelqvist, M. Edmonds, E. Jude, D. Mauricio, L. Uccioli, V. Urbancic, K. Bakker, P. Holstein, A. Jirkovska, A. Piaggesi, G. Ragnarson-Tennvall, H. Reike, M. Spraul, K. Van Acker, J. Van Baal, F. Van Merode, I. Ferreira, M. Huijberts, Diabetologia **51**, 747 (2008).
[17] A. J. M. Boulton, L. Vileikyte, G. Ragnarson-Tennvall, J. Apelqvist, Lancet, **366**, 1719 (2005).
[18] W. J. Jeffcoate, Acta Chir. Belg. **105**, 140 (2005).
[19] J. Larsson, C. D. Agardh, J. Apelqvist, A. Stenström, Clin. Orthop. Relat. Res. **350**, 149 (1998).
[20] M. G. Goldner, Diabetes **9**, 100 (1960).
[21] I. A. Veresiu, S. S. Iancu, C. Bondor, Diabetes Res. Clin. Pract. **109**, 293 (2015).
[22] C. I. Bondor, I. A. Veresiu, B. Florea, E. J. Vinik, A. I. Vinik, N. A. Gavan, J. Diabetes Res. **2016**, 1 (2016).
[23] A. I. Veresiu, C. I. Bondor, B. Florea, E. J. Vinik, A. I. Vinik, N. A. Gâvan, J. Diabetes Complications **29**, 644 (2015).
[24] S. Fosse, A. Hartemann-Heurtier, S. Jacqueminet, G. Ha Van, A. Grimaldi, A. Fagot-Campagna, Diabet. Med. **26**, 391 (2009).
[25] T. S. Ikonen, R. Sund, M. Venermo, K. Winell, Diabetes Care **33**, 2598 (2010).
[26] H. Pham, D. G. Armstrong, C. Harvey, L. B. Harkless, J. M. Giurini, A. Veves, Diabetes Care **23**, 606 (2000).
[27] M. J. Young, J. L. Breddy, A. Veves, A. J. Boulton, Diabetes Care **17**, 557 (1994).
[28] A. J. M. Boulton, R. S. Kirsner, L. Vileikyte, N. Engl. J. Med. **351**, 48 (2004).
[29] International Working Group on the Diabetic Foot, "Prevention and management of foot problems in diabetes: a Summary Guidance for daily practice 2015" (2015).
[30] B. Aulivola, C. N. Hile, A. D. Hamdan, M. G. Sheahan, J. R. Veraldi, J. J. Skillman, D. R. Campbell, S. D. Scovell, F. W. LoGerfo, F. B. Pomposelli Jr, Arch. Surg. **139**, 395 (2004).
[31] G. E. Reiber, L. Vileikyte, E. J. Boyko, M. del Aguila, D. G. Smith, L. A. Lavery, A. J. Boulton, Diabetes Care **22**, 157 (1999).
[32] M. J. Young, A. J. Boulton, A. F. MacLeod, D. R. Williams, P. H. Sonksen, Diabetologia **36**, 150 (1993).
[33] R. J. Hinchliffe, G. Andros, J. Apelqvist, K. Bakker, S. Friederichs, J. Lammer, M. Lepantalo, J. L. Mills, J. Reekers, C. P. Shearman, G. Valk, R. E. Zierler, N. C. Schaper, Diabetes. Metab. Res. Rev. **28**, 179 (2012).
[34] A. Hingorani, G. M. LaMuraglia, P. Henke, M. H. Meissner, L. Loretz, K. M. Zinszer, V. R. Driver, R. Frykberg, T. L. Carman, W. Marston, J. L. Mills Sr, M. H. Murad, J. Vasc. Surg. **63**, 3S (2016).
[35] S. Morbach, H. Furchert, U. Gröblinghoff, H. Hoffmeier, K. Kersten, G. T. Klauke, U. Klemp, T. Roden, A. Icks, B. Haastert, G. Rümenapf, Z. G. Abbas, M. Bharara, D. G. Armstrong, Diabetes Care **35**, 2021 (2012).
[36] O. Nelzen, Phlebology **15**, 110 (2000).
[37] International Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers. Wounds International (2013).
[38] A. F. Fercher, W. Drexler, C. K. Hitzenberger, T. Lasser, Rep. Prog. Phys. **66**, 239 (2003).
[39] N. V. Iftimia, D. X. Hammer, R. D. Ferguson, M. Mujat, D. Vu, A. A. Ferrante, Opt. Express **16**, 13624 (2008).
[40] N. Ukhrowiyah, D. Kurniadi, Suhariningsih,

M. Yasin, Optoelectron. Adv. Mat. **9**, 995 (2015).
[41] B. H. Park, M. C. Pierce, B. Cense, J. F. de Boer, Opt. Express, **11**, 782 (2003).
[42] D. Savastru, E. W. Chang, S. Miclos, M. B. Pitman, A. Patel, N. Iftimia, J. Biomed. Opt. **19**, 056001 (2014).
[43] D. Yudovsky, A. Nouvong, K. Schomacker, L. Pilon, J. Biomed. Opt. **16**, 8, doi:10.1117/1.3535592 (2011).
[44] M. A. Calin, S. V. Parasca, D. Savastru, D. Manea, Appl. Spectrosc. Rev. **49**, 435 (2014).
[45] D. Manea, M. A. Calin, S. Miclos, D. Savastru, R. Negreanu, Rom. Rep. Phys. **67**, 1503 (2015).
[46] R. A. De Blasi, R. Luciani, G. Punzo, R. Arcioni, R. Romano, M. Boezi, P. Mene, Crit. Care **13**, 10 (2009).
[47] E. S. Papazoglou, M. Neidrauer, L. Zubkov, M. S. Weingarten, K. Pourrezaei, J. Biomed. Opt. **14**, 10 (2009).
[48] J. G. Fujimoto, C. Pitris, S. A. Boppart, M. E. Brezinski, Neoplasia **2**, 9 (2000).
[49] V. J. Srinivasan, J. Y. Jiang, M. A. Yaseen, H. Radhakrishnan, W. Wu, S. Barry, A. E. Cable, D. A. Boas, Opt. Lett. **35**, 43 (2010).

*Corresponding author: miclos@inoe.ro