NON-INVASIVE OBJECTIVE ASSESSMENT OF DIABETIC FOOT ULCER HEALING WITH BLOOD PERFUSION AND TISSUE OXYGENATION

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To my beloved parents, thank you.

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ABSTRACT

The high prevalence of the world's population diagnosed with diabetes mellitus, with a significant number suffering from diabetic foot ulcer (DFU), has always been a global concern. Although modern medical technologies are available to assist medical physician in wound diagnosis, the practicability of these techniques have yet to be critically assessed. Only a limited number of biomedical researches have examined the correlation between blood flow and tissue oxygenation in diabetic wounds. This thesis is a pioneering work that aims to develop a reliable diagnostic tool to address the tremendous need for coordinated and efficient DFU management via prediction of relative blood perfusion (τ) and transcutaneous oxygen saturation (S_tO_2). The laser speckle integrated multispectral imaging system is an optical, non-invasive system that is able to provide quantitative and visual information of blood perfusion and tissue oxygen in diabetic ulcer. The estimation of blood perfusion is based on speckle contrast analysis of blood flow whereas the estimation of S_tO_2 parameter is by means of fitting the Extended Modified Lambert Beer model to the collected attenuation data. This system incorporates the use of a 650 nm low power laser diode for *in-vivo* assessment of blood perfusion and wavelength in the visible range of $530-570$ nm to predict tissue oxygenation using *priori* information of hemoglobin's coefficients. A study was conducted on DFU patients recruited from Hospital Sultanah Nora Ismail. The results from this research revealed a slightly higher mean blood perfusion and tissue oxygen level in positive healing wounds than in impaired healing wounds, despite data indicating no statistical significance between these two groups ($\rho = 0.909$ and $\rho = 0.512$ for τ and S_tO_2 data, respectively). This research concludes that a mean blood perfusion index of $1.5\ (\times 10^3)$ and percent S_tO_2 of at least $70\ \%$ are vital during the proliferative phase to ensure progressive healing. The strategies explored in this work can provide quantitative information of changes in blood perfusion with tissue revascularization to evaluate the outcomes of skin grafting procedures in positive and impaired healing diabetic wounds.

ABSTRAK

Kelaziman populasi dunia yang didiagnosis dengan *diabetes mellitus*, dengan sejumlah besar menderita ulser kaki diabetes (DFU), menjadi kebimbangan global sejak beberapa tahun lalu. Walaupun terdapat teknologi perubatan moden untuk membantu doktor perubatan dalam diagnosis luka, kebolehlaksanaan teknik ini belum dinilai secara kritikal. Hanya sebilangan kecil penyelidikan bioperubatan yang mengakaji kaitan antara aliran darah dan oksigenasi tisu pada luka diabetes. Tesis ini merupakan usaha perintis yang bertujuan untuk membangunkan alat diagnostik bagi mengatasi keperluan besar pengurusan DFU yang selaras dan efisien melalui pengukuran perfusi darah relatif (τ) dan ketepuan oksigen transkutan (S_tO_2). Sistem pengimejan bersepadu bintik laser dan multispektral adalah sistem optik tidak invasif yang dapat menyediakan maklumat kuantitatif dan visual oksigen tisu dan peredaran darah dalam ulser diabetik. Anggaran parameter S_tO_2 adalah dengan memadankan model *Extended Modified Lambert Beer* kepada data pelemahan yang dikumpul manakala anggaran perfusi darah berdasarkan analisis bintik kontras aliran darah. Sistem ini menggabungkan penggunaan diod laser kuasa rendah 650 nm untuk taksiran perfusi darah *in-vivo* serta panjang gelombang nampak dalam rangkaian 530 – 570 nm untuk anggaran pengoksigenan tisu menggunakan maklumat *priori* pekali hemoglobin. Kajian dijalankan terhadap pesakit DFU yang direkrut dari Hospital Sultanah Nora Ismail. Hasil kajian ini mendedahkan tahap perfusi darah dan oksigen tisu yang lebih tinggi dalam luka penyembuhan positif berbanding luka penyembuhan terencat walaupun data menunjukkan tiada keertian statistik antara kedua-dua kumpulan ($\rho = 0.909$ dan $\rho = 0.512$ masing-masing untuk τ dan S_tO_2). Kajian ini menyimpulkan bahawa min indeks perfusi darah $1.5\ (\times 10^3)$ dan peratus S_tO_2 sekurang-kurangnya 70 % adalah penting semasa fasa proliferatif untuk menjamin penyembuhan progresif. Strategi yang diterokai dalam kerja ini dapat memberi maklumat kuantitatif perubahan dalam perfusi darah dengan vaskularisasi tisu dalam penyembuhan luka diabetik positif dan terencat.

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LIST OF SYMBOLS AND ABBREVIATIONS

A	–	Light attenuation
C	–	Concentration of absorber, mol L^{-1}
CCD	–	Charge-coupled detector
d	–	Light pathlength, mm
D	–	Aperture diameter, mm
DFU	–	Diabetic foot ulcer
EMLB	–	Extended Modified Lambert Beer
f	–	Frequency, hertz
f_L	–	Focal length, mm
G_0	–	Light attenuation offset
G_1	–	Absorption dependent light attenuation
Hb	–	Deoxygenated hemoglobin
HbO_2	–	Oxyhemoglobin
HeNe		Helium-Neon
I_0	–	Transmitted light intensity
I	–	Detected light intensity
$\langle I \rangle$	–	Mean light intensity
k	–	Speckle contrast
LASCA	–	Laser speckle contrast analysis
NIR	–	Near-infrared
NMRR	–	National Medical Research Register
S	–	Speckle size
S_aO_2	–	Arterial blood oxygen saturation, %
S_tO_2	–	Transcutaneous oxygen saturation, %
SNR	–	Signal to noise ratio, dB
T	–	Light transmittance
T_H	–	Total absorbers concentration, mol L^{-1}

T_s	–	Exposure time, second
v	–	Velocity, ms^{-1}
ε	–	Molar extinction coefficient, $mm^{-1}\,M^{-1}$
$\Delta\varepsilon$	–	Absorptivity difference, $mm^{-1}\,M^{-1}$
λ	–	Wavelength, nm
μ_a	–	Absorption coefficient, mm^{-1}
μ_s	–	Scattering coefficient, mm^{-1}
ρ	–	Probability value
ρO_2	–	Partial pressure of oxygen, mmHg
σ	–	Standard deviation
τ	–	Correlation time
$\varnothing$	–	Diameter, mm

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CHAPTER 1

INTRODUCTION

1.1 Background of the study

A retrospective study by the World Health Organization (WHO) based on data sources collected from 221 countries and territories had estimated at least 451 million adults aged 18 – 99 years old worldwide diagnosed with diabetes mellitus as of the year 2017 [1]. This figure was expected to project up to 693 million by the year 2045. A majority of diabetes cases were identified among those living in low- and middle- income countries, with Western Pacific region having the highest prevalence of total global diabetes population. China was quoted as having the highest number of population with diabetes with 98.4 million adults diagnosed, followed by India with 65.1 million [2]. Likewise in Malaysia, a statistical study conducted by the National Health and Morbidity Surveys (NHMS) in the year 2011 reported at least 15.2 % of adults aged 18 years old and above suffered from diabetes mellitus, which accounted for up to 2.6 million of the population [3]. The prevalence of this disease was expected to escalate to 21.6 % by the year 2020. Although there was no significant difference in prevalence between gender, a large variation was observed between the three main ethnic groups in Malaysia with the highest prevalent among Indians at 24.9 %, followed by Malays at 16.9 % and finally, Chinese at 13.8 % [4]. Specifically, a retrospective study by Raja [5] stated that diabetic foot ulcer (DFU), a microvascular complication of diabetes mellitus, constituted 15 % of all diabetes cases. Of this figure, approximately 20 % of DFU cases are the results of peripheral and autonomic neuropathy as well as diabetic angiopathy, which, if left untreated can lead to foot infection and amputation of the lower extremity. Socio-economic status, living environment and eating habits are among the factors linked to the radical rise in diabetes cases worldwide [6]. The global health expenditure for diabetes patients in 2017 was estimated to be USD 850 billion, which was twice the expenditure of patients without diabetes [1]. Moreover, the number of deaths attributed to diabetes in the same year was reported to be approximately five million. The occurrence of this disease had been deemed to be increasingly alarming as it had left deleterious effects on impacted patients and their families both emotionally and financially.

Thus far, biomedical researchers worldwide have proposed various techniques to overcome the tradeoffs of standard clinical practices. A reliable and non-invasive technique for quantitative measurement of DFU healing progress has been a subject widely researched in recent years. The conventional method of bedside clinical assessment by means of subjective visual assessment, although can be performed immediately at no cost, has otherwise turned out to be unreliable and inaccurate in terms of diagnosis [7]. Over the years, several techniques to predict wound healing status have been introduced. These techniques, for example, range from punch biopsy method for bacterial load analysis, which is not only invasive in nature but also time-consuming [8], to non-invasive optical imaging approach such as Raman spectroscopy technique that involves tedious tabulation works [9]. Moreover, the commonly practiced laser Doppler flowmetry is only able to provide information on blood flow perfusion measurement in tissue [10]. Therefore, the limitations of the use of these techniques are critically assessed [11].

Meanwhile, modern clinical practice of diagnosing and monitoring the progression of diseases involves the use of medical imaging techniques. Among the commonly used modalities at present are magnetic resonance imaging (MRI), computerized tomography (CT) scan, positron emission tomography (PET) scan and single photo emission computed tomography (SPECT) scan [12-14]. These cutting edge imaging techniques are proven to be highly beneficial in detecting any abnormalities in the tissue structure based on two-dimensional (2D) or three-dimensional (3D) images that produce very detailed anatomic information of the scanned body. However, these machines are costly in price and require the use of contrast agents or radioactive tracers to be administered into the patient's body, hence, limiting the application of these approaches on patients with critical illnesses since the use of contrast agents has side effects likely not recommended for pregnant women [15, 16].

Early prognosis and evaluation of DFU recovery progress can be performed using quantitative information deduced from changes in skin microcirculatory activities namely tissue oxygenation and blood perfusion level at different stages of wound healing. Sufficient blood perfusion and oxygen supply to wound regions are likely to guarantee positive healing progress, hence the requirement of a systematic prognosis system to provide clinical information of diabetic ulcer microcirculatory status. Proper wound care management is not only vital to achieve full recovery of the anatomical functionality; it also contributes to the reduction in medical cost in the long period. This is possible given that medical practitioners are provided with adequate information as a guideline to identify detrimental factors leading to delay of healing in DFU and immediate actions are undertaken to overcome these problems.

Awareness of this matter has led to the rise in biomedical research to come up with an applicable diagnosis tool that can provide detailed *in-vivo* information of wound based on the optical properties of scattering and absorbing media in the biological skin tissue. This is viable using a spectroscopic and spatially resolved speckle interference pattern obtained from a speckle integrated multispectral imaging system. Laser speckle contrast imaging is a technique which has advanced over the years, with its application ranging from imaging of multimodal skin layers, cerebral cortex, and retina using light of wavelength 633 nm [17, 18]. The fundamental basis of this concept is based on the interference pattern of light reflected or scattered from the illuminating surface, which in return produces a granular effect known as the laser speckle. The movement of the speckle pattern is concurrent to the movement of an object, prompting the idea of the most significant application of speckle fluctuation initiated by blood flow velocity during the mid-1970s [19].

This work sets out to employ laser speckle integrated multispectral imaging for concurrent measurement of blood perfusion and oxygen saturation mapping of foot ulcers. The best guess of these required values is via a heuristically developed fitting model predicted based on light absorption properties and time-integrated speckle pattern produced by laser light interference between the light source and refraction in the medium. To further verify the effectiveness of this method, efforts are undertaken to collaborate with a hospital where a group of DFU patients was recruited as volunteers to support this study with solid scientific and clinical data. This study presumes the proposed quantitative values of wound healing parameters and the developed strategies can assist surgeons in determining the uncertainty of wound closure through proper classification of chronic diabetic foot ulcers healing status.

1.2 Problem statement

There is a tremendous need for coordinated and efficient wound healing management in DFU patients nationwide. The predominance of DFU among patients suffering from diabetes has led to limitations in daily activities as well as reduced living quality. In some cases, chronic DFU can cause morbidity and lower limb amputation that results in permanent disability and also contributes to emotional depression. The call for proper management and assessment of diabetic wound is highly sought after with the increase in the use of healthcare centers and hospitals. As the economy continues to decline and the cost of medical fee increases, the need for a more cost-effective and systematic wound management solution expands throughout the nation [20]. Undoubtedly, there are many medical options for accurate diagnosis of DFU, but these options lack in terms of suitability and can be costly in price [15, 16]. Numerous methods have been proposed in the biomedical field of study to improve the prediction accuracy of wound healing progress, taking into account aspects such as time, cost and consistency [7, 21, 22]. However, these works were unable to concurrently image blood flow and tissue oxygenation status during the different phases of DFU healing progress. As such, a non-invasive and detailed approach to study the optical properties of the biological skin tissue is highly sought after. The laser speckle contrast technique has been proven capable in measuring cutaneous blood flow whereas multispectral imaging is a non-invasive approach to acquire optical properties of biological tissue [23-25]. No work, has, thus far, combined the two technologies. In addition, assessment of wound should include a complete understanding of wound pathology, environmental factors that affect healing and intense study on tissue remodeling. These environmental factors, which include microenvironment factors of that within or surrounding the wound such as blood flow, moisture, nutrient availability and bioburden factors, e.g. biofilm concentration are among the factors accounted for when ensuring a conducive environment for healing [26]. This allows a strategic treatment to be assigned accordingly to each patient bearing these factors to ensure a progressive healing. A strong correlation

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