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REVIEW ARTICLE

# Biophotonics methods for functional monitoring of complications of diabetes mellitus

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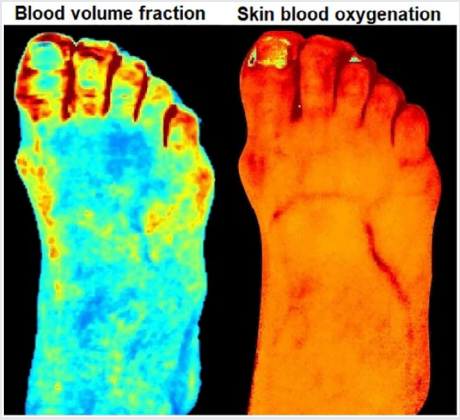
## Abstract




The prevalence of diabetes complications is a significant public health problem with a considerable economic cost. Thus, the timely diagnosis of complications and prevention of their development will contribute to increasing the length and quality of patient life, and reducing the economic costs of their treatment. This article aims to review the current state-of-the-art biophotonics technologies used to identify the complications of diabetes mellitus and assess the quality of their treatment. Additionally, these technologies assess the structural and functional properties of biological tissues, and they include capillaroscopy, laser Doppler flowmetry and hyperspectral imaging, laser speckle contrast imaging, diffuse reflectance spectroscopy and imaging, fluorescence spectroscopy and imaging, optical coherence tomography, optoacoustic imaging and confocal microscopy. Recent advances in the field of optical noninvasive diagnosis suggest a wider introduction of biophotonics technologies into clinical practice and, in particular, in diabetes care units.

**KEYWORDS**
biomedical photonics, diabetes mellitus, imaging, optical noninvasive diagnostics, spectroscopy

## 1 | INTRODUCTION

Studies related to diabetes mellitus (DM) are attracting increased attention from scientists around the world. DM is a group of chronic long-term diseases characterized by various metabolic disorders. There are two main forms of diabetes: type 1 and type 2 diabetes, however, diabetes can also occur during pregnancy and under the influence of other conditions. The clinical course of diabetes is characterized by a state of hyperglycemia resulting from insulin deficiency or insulin resistance. Chronic hyperglycemia leads to blood vessels damage, which causes the development of diabetes complications [1, 2].

Over the past few years, the prevalence of diabetes has reached alarmingly high levels. The number of diagnosed patients with this disease already amounts to approximately half a billion worldwide, and this number will only grow in the near future, according to forecasts [3].

Owing to the increasing prevalence of the disease, complications of diabetes is now considered one of the most important problems of modern healthcare. According to experts, almost every patient with diabetes will develop at least one or more complications throughout his or her life [2, 4]. Complications of diabetes range from acute, life-threatening conditions, such as severe hypoglycemia or ketoacidosis, to chronic, debilitating complications affecting many organs and organ systems, such as retinopathy, nephropathy, neuropathy and cardiovascular disease. Chronic complications of diabetes are formed under the influence of prolonged exposure to high levels of glucose in the body [2]. They are associated with disorders of the cardiovascular and nervous systems. Ultimately, these complications can lead to severe vision loss and blindness, end-stage of renal disease and need for hemodialysis or transplantation, development and infection of diabetic ulcers, amputations, heart failure, stroke and so on. Currently, it has been demonstrated that the length and health-related quality of life of diabetic patients are determined by the presence and severity of chronic complications of this disease, as well as the quality of their treatment [5, 6]. In this regard, there is an urgent need for the early detection and prevention of the development of diabetic complications.

Biophotonics methods represent a viable solution to this problem. Various spectroscopy and imaging technologies can provide information on the optical properties of skin, which are directly related to its blood supply, degree of oxygenation and the presence of chromophores [7]. Table 1 presents the various methods of biophotonics and their application in studies of DM complications.

Thus, biophotonics present unique possibilities for both structural and functional analysis of biological tissues, as well as early and noninvasive diagnosis and monitoring of the effectiveness of the therapy in various diseases. Recently, there has been a surge of interest in the use of optical technologies in diabetes. Several reviews have been published in this area, including articles examining the change in the optical properties of biological tissues related to DM [67], a review of technologies for imaging ulcers [68], and technologies for studying microcirculation in DM [23]. To the best of our knowledge, there are no review articles that focuses on biophotonics methods for investigating all the DM complications, including retinopathy, neuropathy, microangiopathy and diabetic ulcers.

This article aims to combine the accumulated experience in the field of optical noninvasive diagnosis of diabetes complications and provide a comprehensive review of the literature in this area.

**TABLE 1** Body parameters evaluated by biophotonics in the diagnosis of diabetes complications

| Biophotonics method | Characteristics assessed |
|---|---|
| Capillaroscopy | Vascular bed morphology [8–10] and blood flow velocity [11] |
| Laser Doppler flowmetry and imaging | Blood flow [12–16] and blood flow oscillations [17–20] |
| Laser speckle contrast imaging | Blood flow, diabetic wounds [21–24] |
| Diffuse reflectance and near-infrared spectroscopy and imaging | Tissue oxygen saturation, chromophores content, blood volume and diabetic wounds [25–32] |
| Hyperspectral imaging | Chromophores content, the thickness of the epidermis, blood filling, oxygen saturation, wound development prediction and healing assessment [24, 33–36] |
| Fluorescence spectroscopy and imaging | Accumulation of AGE [37, 38], metabolic activity of tissue [39, 40] and diabetic wounds [41] |
| Optical coherence tomography | Retinal morphology [42–47] retinal nerves condition [48, 49], |
| | retinal perfusion measurement [50–53], protein glycation [54–57] |
| Confocal microscopy | Corneal morphology, corneal nerves condition [58–62] |
| Raman spectroscopy | Collagen degradation, accumulation of AGE [63] and protein glycation [64, 65] |
| Terahertz spectroscopy | Water content [66] |

In this review, the following optical technologies for studying DM complications will be considered: capillaroscopy, dynamic light scattering methods (laser Doppler flowmetry [LDF] and imaging, laser speckle-contrast imaging [LSCI]), diffuse reflectance spectroscopy (DRS) and imaging, fluorescence spectroscopy and imaging, optical coherence tomography and confocal microscopy. We specifically focused on methods for noninvasive diagnosis and monitoring of diabetes complications, not including optical studies of blood glucose levels.

## 2 | OPTICAL APPROACHES IN DIAGNOSTICS

### 2.1 | Capillaroscopy

Capillaroscopy is a convenient method to assess the morphology of the vascular bed and its changes in vivo as the disease develops. To conduct the capillaroscopic studies, a microscope with a lower or higher magnification is usually used, to obtain panoramic images of the capillary bed or enlarged images of individual capillaries and their groups, respectively. The studies are mainly carried out in the nail bed since the capillary arc extends parallel to the skin surface. Therefore, it is possible to monitor the blood flow in the capillaries at a sufficiently large increase, while in other parts of the skin the capillaries are perpendicular to the skin surface. During the study, the hand is usually placed on the examination table at heart level and a drop of immersion oil is deposited on the nail bed, to increase the transparency of the skin [69]. The inner surface of the lower lip is also commonly researched for capillaroscopy [70], although the research there is associated with more significant methodological difficulties.

Capillaroscopy has been used to study the state of microcirculation since the 19th century. Historically, this technique is the most widespread in the studies of vascular disorders in rheumatic diseases [69], although the spectrum of application of this technology is quite extensive. Furthermore, capillaroscopy can be used to estimate the number of visualized capillaries in the nail bed, density of the capillary network, presence of tortuous capillaries and hemorrhages and diameters of the arterial and venous parts of the capillary [71]. These are important diagnostic parameters of the condition of the cardiovascular system. To evaluate these parameters, static images of the capillary network are usually recorded with subsequent analysis of the photographs.

Modern video capillaroscopy systems have high-speed cameras and side lighting with an average of 2 to 4 high-brightness LEDs with a wavelength of 520 to 530 nm, which provides maximum contrast of the images of the capillary network due to the absorption of light by blood in this wavelength range.

Diabetes is one of many diseases leading to abnormalities in the morphology and physiology of the capillary bed. Numerous studies have shown that patients with diabetes demonstrate microvascular changes, which were recorded by the capillaroscopy method. Among such changes, tortuosity, dilated capillaries and a decrease in the capillary network density are distinguishing features [8, 72–76]. Figure 1 presents the altered structure of the capillary bed of a patient with DM obtained by capillaroscopy.

In the studies of children and adolescents with diabetes avascular zones and hemorrhages were found [77]. In addition, it was shown that the presence and severity of microvascular changes largely depends on the presence of DM complications, duration of the disease and quality of metabolic control [78, 79]. Attempts have also been made to evaluate the difference in capillaroscopic pictures of patients with type 1 and type 2 diabetes; however, the results of these studies are contradictory [9, 78].

A promising area of research is the dynamic assessment of the velocity of blood flow throughout the vessels in control and diabetic subjects, as well as the assessment of changes in this parameter when exposed to external factors (e.g., temperature and occlusion). Some studies have already shown that blood flow velocity is significantly reduced in patients with diabetes compared with healthy controls, especially in those with complications [8, 11]. Moreover, the value of the peak blood flow velocity during reactive postocclusive hyperemia is reduced in patients with diabetes [8]. Recent advances in signal processing for high-speed video capillaroscopy have shown the possibility of evaluating blood flow fluctuations in individual capillaries associated with physiological regulation of blood flow [80] (a more detailed description of blood flow fluctuations is presented in the following section). Research in this area is promising for the diagnosis of diabetes complications.

### 2.2 | Dynamic light scattering

The basic principles of dynamic light scattering (DLS) are based on phenomena such as frequency shift and intensity fluctuations of light propagated through a turbid tissue-like scattering medium containing moving particles. This method is typically based on the illumination of biological tissues by continuous laser radiation and simultaneously recording the fluctuations of the intensity of the scattered light utilizing a single-mode optical fiber or camera [81]. The blood flow velocity is calculated according to the field autocorrelation function.

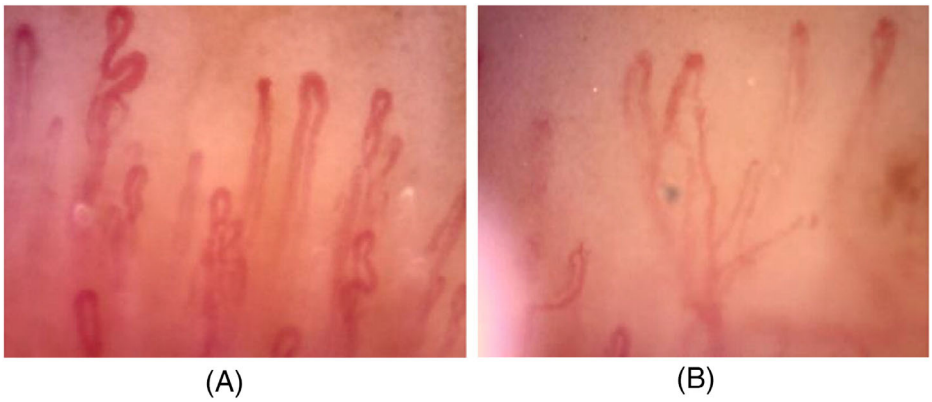



**FIGURE 1** Capillaroscopy of a diabetic patient: altered vascular structure characterized by tortuous, cross-linked, and dilated capillaries, A, as well as ramification and a slight decrease in capillary density, B [10]. Reproduced with permission of Elsevier

DLS methods have been used to measure the velocity of moving particles since the 1960s [82]. Several methods for measuring the velocity of both flowing and diffusing particles for single scattering cases have been developed [83–85], and a DLS theory was developed for a multiply scattering medium [86–88]. Among the DLS-based methods, LDF and LSCI are extensively used for monitoring the blood flow in skin for various physiological and pathological conditions [89–94]. In DLS techniques, red (630-650 nm) and near-infrared (750-1100 nm) wavelengths of the laser source are usually used (most commonly used semiconductor lasers).

### 2.2.1 | Laser Doppler flowmetry

Currently, LDF is a widely used method for the in vivo assessment of the state of microcirculatory blood flow. Laser Doppler measures the total local microcirculatory blood perfusion. This technique is based on tissue sensing by laser light and analysis of the light scattered by the tissue. Light impinging on moving red blood cells undergoes a Doppler shift in frequency while light hitting static objects remains unchanged.

Numerous studies have been conducted using LDF to assess peripheral arterial disease (PAD) in diabetes; both monitoring and imaging technologies were used to evaluate the dynamics of blood flow at an individual point and over a larger area, respectively. The results of the studies on peripheral blood flow under basal conditions are controversial. Some studies agree that there are no statistically significant differences in the perfusion parameters between the groups of patients with diabetes and healthy controls, although the LDF signal in patients is lower in absolute values [95–97]. In contrast, other studies note significantly higher values of the microcirculation index in diabetics [12, 98, 99]. Among the latter, the results are usually associated with the effect of long-term sympathetic neuropathy on the microcirculatory function, which causes an increase in cutaneous blood flow, especially in the lower extremities [100, 101].

When conducting measurements using the LDF method, important diagnostic information about the regulation of the microvasculature by various body systems, including nervous and humoral regulation, can also be obtained. The recorded signal can be decomposed into its constituent oscillatory components using wavelet analysis. Previous studies have noted the following oscillatory components and their physiological causes [102, 103]: frequency intervals of 0.005 to 0.0095 Hz and 0.0095 to 0.021 Hz correspond to the regulation of blood flow by endothelium cells through the release of nitric oxide and other vasoactive substances into the vessel lumen, respectively; range 0.021 to 0.052 Hz is associated with the influence of microvascular innervation; fluctuations with a frequency of 0.052 to 0.145 Hz correspond to the influence of vascular-smooth-muscle activities; 0.45 to 1.6 Hz and 0.2 to 0.45 Hz frequency bands carry information about the influence of heart rate and thorax movement on the peripheral blood flow, respectively.

One of the main drawbacks imposed on the LDF technique is the lack of absolute perfusion units and the high heterogeneity of the signal between the subjects and within the same subject when measured from different points of the body. Nonetheless, LDF can have excellent temporal resolution. In this regard, the method has found wide applications in the analysis of the microcirculatory bed reaction to various physiological and pharmacological stimuli. Occlusion, orthostatic, iontophoretic and local heating tests are used to assess microcirculatory disorders in diabetes. Acetylcholine (Ach) and sodium nitroprusside are usually used as pharmacological stimuli. In a study on the microcirculatory system reactivity using pharmacological tests, a significant decrease in the maximum vasodilation in DM patients compared with the controls was observed [104].

Of the physiological effects, local thermal exposure or local heating test is most often used. The popularity of

this test could be explained by the fact that it is painless, easy to use and noninvasive. Local heating allows evaluation of two vasodilation mechanisms: the reflex reaction of the local sensory nerves and endothelium-dependent vasodilation, which occurs during prolonged heating [105]. A recent review and meta-analysis of articles studying the use of LDF in conjunction with a local heating test for assessing microcirculation in diabetes [16] showed that most studies indicated reduced vasodilation in patients with diabetes in response to local heating. In addition, this parameter was even more reduced in a group of patients with diagnosed diabetes complications (such as diabetic dermopathy, neuropathy or angiopathy) compared to patients without complications [41, 106]. However, it should be noted that these studies are significantly limited by the fact that the conditions for a local heating test, in particular, are not standardized, and different authors apply different experimental conditions. The studies used different heating modes with different maximum temperatures. Additionally, the rate of tissue heating was not indicated in some of the studies, and different durations of the heating stage were used in different protocols. In general, a significantly reduced level of the LDF signal can be noted in patients with diabetes under maximum vasodilation caused by heating [12, 13, 16, 20, 107, 108].

The assessment of reactive postocclusion hyperemia (PORH) in arterial occlusion is also a widely used test to assess the state of microcirculatory blood flow in various pathological conditions, including diabetes. A positive correlation between the time to peak during PORH and the presence of active or past foot ulcers was found in subjects with diabetes by means of LDF [109]. Moreover, it has been observed that the restoration of the initial blood flow after PORH is slower in subjects with diabetes [104].

Although the analysis of blood flow fluctuations registered by the LDF in patients with diabetes is of considerable scientific interest, relatively few studies have been undertaken in this area. Patients with diabetes were found to have impaired vasomotion with a frequency of 0.1 Hz [17], which corresponds to the effect of sympathetic activity. It has been suggested that such abnormalities in blood flow regulation might be symptoms of early sympathetic dysfunction and could precede sympathetic neuropathy [18, 110].

In our studies, we also demonstrated differences in the LDF signals between healthy subjects and patients with diabetes under normal temperature conditions and local heating [19, 20]. It was found that patients with DM have a lower vasodilation rates and a less pronounced response in the frequency range close to 0.14 Hz, which is consistent with previous studies by other authors [111].

Some studies indicate a tendency toward a decrease in vascular function in relatives of patients and volunteers with impaired glucose tolerance [95]. A recent study conducted with LDF confirmed a gradual change in parameters from the control group to the prediabetic and diabetic group [112]. The deterioration of microvascular function was also found in individuals with metabolic syndrome [113].

In addition to the limitations indicated above in the studies of microcirculation by the LDF method, poor standardization of LDF equipment can contribute to circumstances that prevent its wider use in the clinic, which greatly complicates the comparison of the results obtained by different authors.

### 2.2.2 | Laser Doppler perfusion imaging

As mentioned above, one of the distinguishing features of skin microcirculation is its huge heterogeneity. Single-point measurements of LDF can have significant differences when carried out even at a short distance. To overcome this problem, laser Doppler perfusion imaging (LDPI) technology was developed. The first implementation of this technology used a moving mirror that changed the direction of the laser and scanned the tissue point by point, so that the blood flow map could be restored [114, 115]. At present, full-field LDPI systems are proposed and are the objects of active research. The method has found wide application in the assessment of wound healing, including wounds arising from diabetes.

In addition to wound studies, LDPI together with various functional influences was used to evaluate other disorders in diabetes. Using LDPI and local temperature effects, impaired nervous function was shown in patients with diabetes [14]. The method was also used to study the effect of metformin administration on changes in microvascular function in a nondiabetic population [15]. The study included evaluation of microvascular function with vasoactive substances and iontophoresis, and it was aimed at determining the effectiveness of metformin in improving the endothelial function in nondiabetic subjects. At the end of the study, the metformin-treated subjects showed a clear improvement in ACh response.

### 2.2.3 | Laser speckle contrast imaging

Laser speckle contrast imaging (LSCI) is another powerful dynamic light scattering technique allowing noncontact full-field real-time visualization of flows. LSCI for biomedical applications is now gaining increasing

attention. In LSCI information about blood flow is obtained by analyzing the speckle contrast variations [116]. Light scattered on the sample falls on the camera, where speckles are recorded. Speckles are formed by interference between photons reaching the same pixel after passing through different paths. The contrast ratio is related to the speed of moving particles causing blurring of the spot, which characterizes the blood flow intensity in biological tissues.

Although this technology has been used to assess the state of blood flow in various areas of medicine, currently, it is rarely used to study microcirculation in diabetes. It was previously shown that LSCI has excellent spatial and temporal resolution, as well as reproducible measurement results [117]. Most studies using LSCI were aimed at studying the state of cerebral [118, 119] and retinal blood flow [120–122]. These sites are most convenient for research as closely lying vessels provide a higher signal-to-noise ratio. Later, this technology was applied in surgical interventions [123, 124].

Recently, LSCI was used in the study of endothelial function in patients with type 1 diabetes [22]. The study used acetylcholine and occlusion tests, and it was found that, in patients, endothelium-dependent vasodilation was significantly reduced in response to both stimuli.

LSCI was successfully applied in the studies of wound healing both in animal models [125, 126] and patients with DM [21]. Figure 2 presents a color photograph of a foot with diabetic ulcers and the corresponding LSCI image.

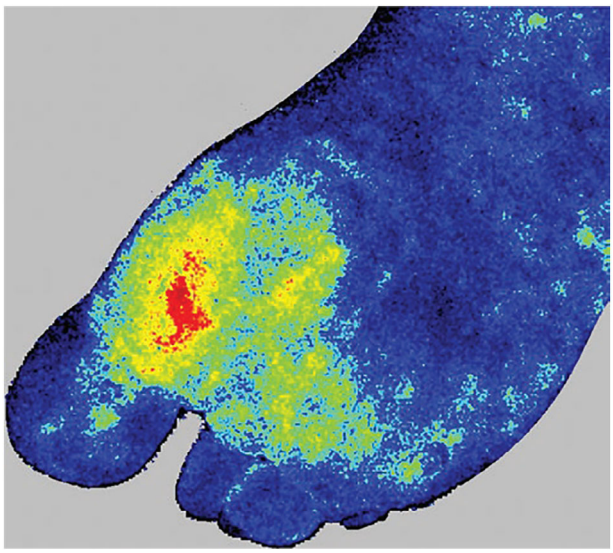


**FIGURE 2** Laser speckle-contrast imaging image of a diabetic foot with an active ulcer in the process of healing [24]. Reproduced with permission of Springer Nature

However, LSCI technique, like other DLS methods, is still suffering from some critical drawbacks. The major one is the significant temporal and spatial variability of the measurements. The temporal variability is usually related to the intrinsic nonstationarity of microcirculation and associated complex dynamics within biological tissue itself, which is also known as, so-called "biological zero" [127]. Although methods for analyzing the dynamics of the LSCI signal were presented [128], there is the absence of a standardized quantitative relationship with the real physiological parameters of blood flow, expressed in the SI units. Whereas, currently available LSCI devices are able to observe only the relative blood changes with no quantitative scale of measure, resulting in usage of the arbitrary units. Another major drawback is associated with the approximate account of the detected light scattered with biological tissues, especially in respect to the finite observation time in the statistical sense, known as ergodicity [129–131].

## 2.3 | Diffuse reflectance spectroscopy

DRS has widespread application in medicine. Many studies have used the method to separate malignant and normal tissues in various areas of oncology [132, 133]. An analysis of the changes in the diffuse reflection of tissues can provide information about their morphological and physiological state.

DRS techniques have been implemented to assess the peripheral blood flow and oxygenation saturation state. The method is able to provide continuous noninvasive measurement of changes in the oxygenated ($cHbO_2$) and deoxygenated (cHb) hemoglobin concentration. The studies have shown that some parameters obtained by DRS significantly correlate with measurements of the ankle-brachial index [134], which is a commonly used parameter for assessing the risk of developing diabetes complications [135].

The DRS method has been used in the diagnosis of diabetes-related blood flow disorders for over 15 years. A decrease in the level of blood flow in patients with type 1 diabetes compared with healthy control was shown in the basal state and during exercise [25]. Impaired blood flow while exercising was also shown in type 2 diabetic patients regardless of the presence or absence of peripheral arterial occlusive disease [26]. Significant decrease in the total hemoglobin concentration was observed by DRS in diabetic subjects compared to a control group [28].

The method also found use in the evaluation of foot ulceration and wound healing processes. Usually, when diagnosing the state of oxygenation by this method, an

estimate of the area under the curve of the diffuse reflectance spectrum is used [136]. Some authors propose a ratio of the diffuse reflectance at different wavelengths as a diagnostic parameter. Usually, isobestic points of oxy- and deoxyhemoglobin are selected for these purposes [27]. By applying this approach, changes in the level of tissue oxygenation were studied to differentiate patients with different severities of complications [29] and to predict the healing process of diabetic ulcers [27].

Near-infrared spectroscopy (NIRS) is also a widespread technology for accessing cutaneous oxygen concentration. It was proposed in 1977 [137] and was widely used to estimate blood circulation in the brain and other organs [138–140] in normal and pathological conditions. NIRS utilizes red or near-infrared light to probe the tissue and analyzes the absorption of light on the specific wavelengths, providing information on the total hemoglobin, oxyhemoglobin, deoxyhemoglobin concentrations and tissue oxygen saturation.

NIRS is widely used in the diagnosis and evaluation of the diabetic foot ulcers treatment. Previous studies have shown that NIRS has the potential to predict the diabetic ulcers outcome [30]. The ability of NIRS to differentiate healing and nonhealing ulcers based on the degree of absorption of near-infrared light [31], which is associated with the concentration of hemoglobin, was shown.

In recent studies related to diabetes, NIRS was further developed. Noninvasive wearable wireless devices that implement this technology are being developed to visualize the condition of ulcers at home [32].

## 2.4 | Hyperspectral imaging

Hyperspectral imaging (HSI) is a modern implementation of the DRS method providing information about the tissue oxygenation state. It is able to detect systemic and local microcirculatory changes associated with DM [141]. The technology is most commonly used to analyze the development of wounds, including diabetic ulcers and the results of burns [68]. To implement hyperspectral measurements, a series of images of the object under the study is registered in narrow frequency ranges, forming a hypercube. The hypercube has two spatial coordinates ($x$, $y$) and one spectral ($\lambda$). The analysis of the data contained in the hypercube allows one to assess the content of chromophores in the biological tissue studied, thickness of the epidermis, blood filling and oxygen saturation. Figure 3 shows visible and hyperspectral images of a foot taken with the use of HSI.

The studies conducted using this technology have shown the ability of the method to evaluate the effectiveness of the diabetic ulcer treatment, and predict their development even before they appear. The study carried out by Yudovski et al. showed that by using HSI, it was possible to register the changes in the epithelium thickness that precede the formation of an ulcer [142]. The visible images and oxygen saturation maps from a patient with a developing diabetic foot ulcer are shown in Figure 4.

The study conducted by Khaodhiar et al. investigated the diabetic wound healing process over 6 months using hyperspectral medical technology [33].

The study was conducted on patients with type 1 diabetes and registered values corresponding to concentrations of oxy- and deoxyhemoglobin with subsequent calculation of the healing index. It was shown that HSI successfully distinguishes between healing ulcers and ones that failed to heal. Another study aimed at studying the healing of diabetic ulcers through HSI included patients with type 1 and type 2 diabetes [34]. The tissue oxygenation maps were constructed from oxy- and deoxyhemoglobin values determined for each pixel in the image. Linear discriminant analysis was used to calculate the healing index, by separating healed and unhealed ulcers. It was concluded that the technique could accurately predict wound healing in advance, providing information necessary for treatment and monitoring of diabetes complications.

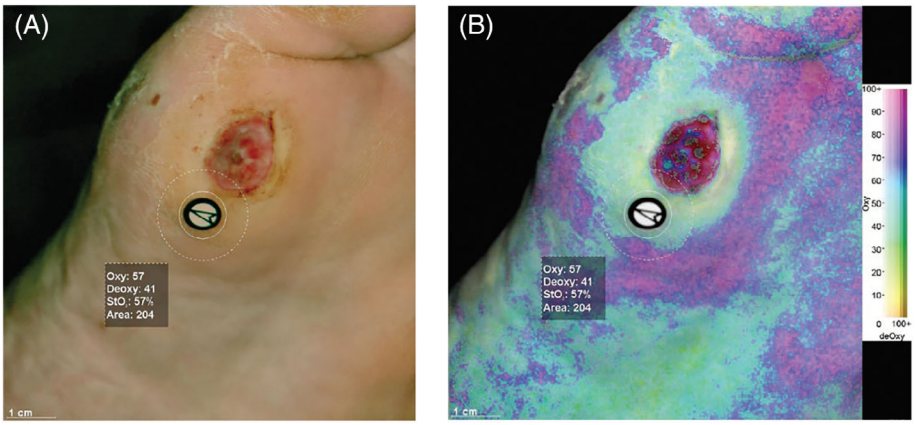



**FIGURE 3** A, Visible and B, hyperspectral images of a diabetic foot ulcer taken with the hyperspectral imaging system [24]. Reproduced with permission of Springer Nature

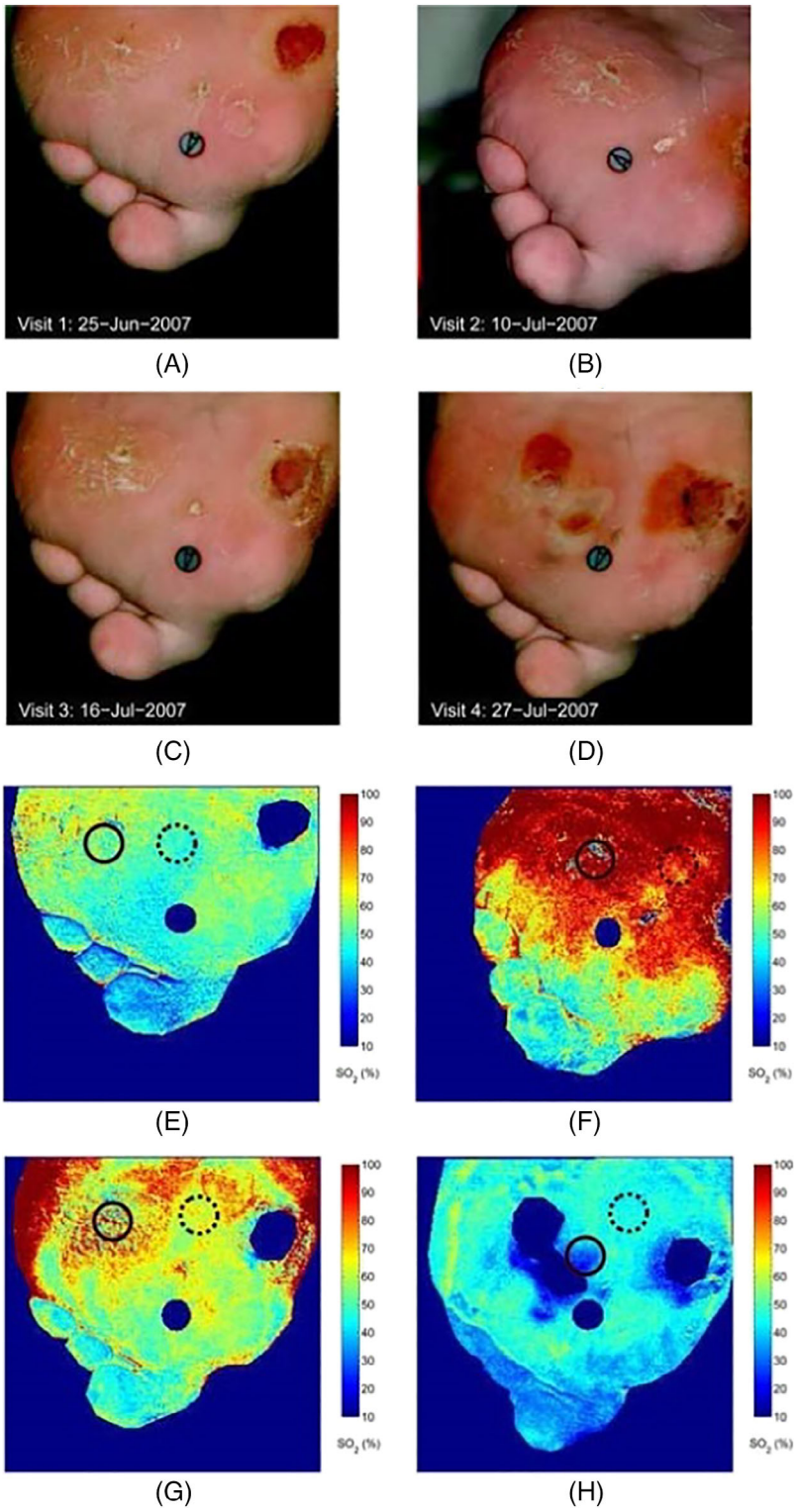



**FIGURE 4** Visible images, A-D, and corresponding oxygen saturation maps, E-H, of the foot of diabetic subject with developed ulcer [36]. Reproduced with permission of John Wiley and Sons

In summary, HSI can accurately predict ulcer healing in a few months and identify ulcers that are at risk of not healing, and therefore, could be used to screen for lower-extremity complications due to diabetes. Emerging technologies for the collection and analysis of hyperspectral data [143], including artificial intelligence systems, suggest an even wider introduction of this technology in clinical diagnostics.

## 2.5 | Fluorescence spectroscopy and imaging

The accumulation of advanced glycation end-products (AGEs) and oxidative stress are among the key mechanisms for the development of diabetes complications [144, 145]. The AGEs are proteins and lipids that become glycated as a result of exposure to sugars and known as

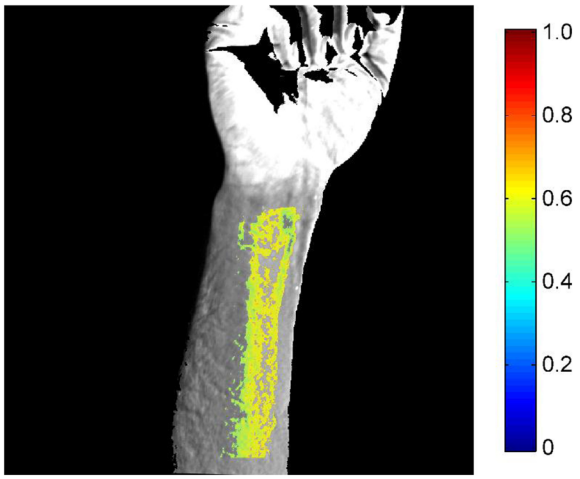



**FIGURE 5** Example of a grayscale AGE-index image of the volar side of the arm detected by a multiphoton fluorescence imager [148]. The colored region indicate the region of interest selected for the AGE-index calculation. Reproduced with permission of Elsevier

glycotoxins due to their harmful effect. By accumulating in the body, AGEs start the process of protein cross-linking, in particular, in collagen, myelin and hemoglobin molecules. The glycated proteins fluoresce when irradiated with UV light. Figure 5 shows the fluorescence of AGE in the arm by multiphoton fluorescence spectroscopy. In the 1990s, the fluorescence of cross-linked proteins was shown to increase significantly with aging and in patients with diabetes [146]. In the early stages, the AGE fluorescence studies were performed in blood and urine samples and skin biopsies. The cross-linked protein fluorescence has been shown to be higher in patients with complications of diabetes, particularly kidney disease, compared to those without complications [147].

Meerwaldt et al. reported one of the first studies of noninvasive AGE-accumulation measurement using fluorescence spectroscopy [37]. They validated skin autofluorescence measurements against the results of biochemical analyses of skin biopsies in healthy subjects and patients with DM but with no clinical signs of complications (see Figure 6). In the skin of patients with DM, the AGE autofluorescence significantly correlates with the long-term level of glycated hemoglobin (HbA1c) and not with its current level [149, 150]. Thus, the level of tissue AGEs reflects long-term metabolic disorders in diabetes and can be considered an indicator of "glycemic memory." For this reason, many studies have indicated that the level of AGE fluorescence can be an independent predicator of microvascular complications, neuropathy and renal disease.

Gerrits et al. studied 881 patients with type 2 diabetes to determine the feasibility of skin fluorescence

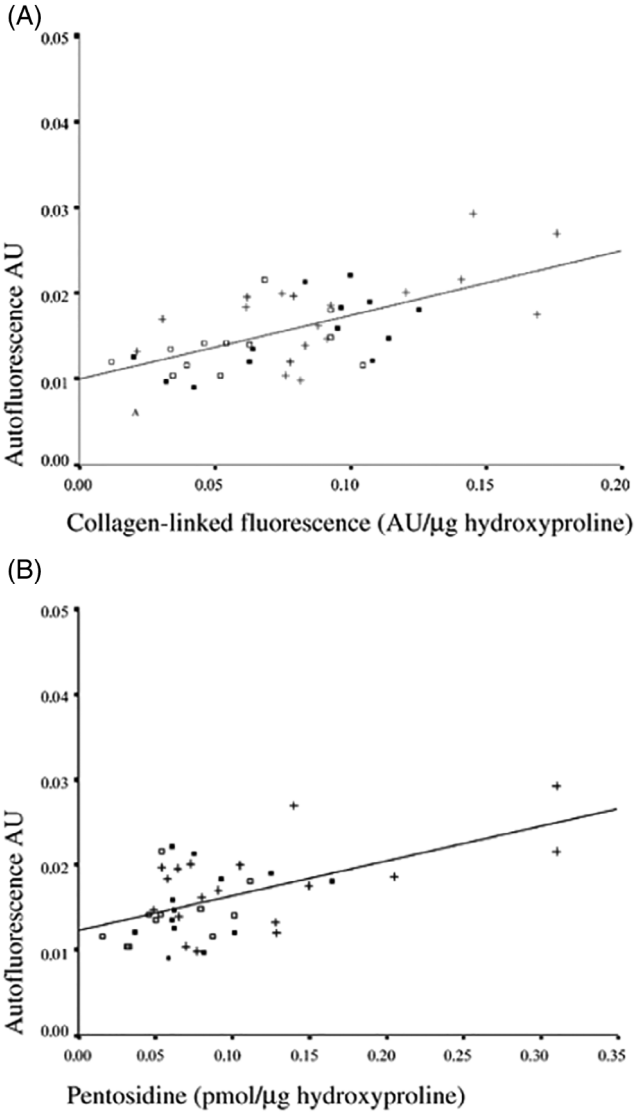



**FIGURE 6** A, Collagen-linked and, B, pentosidine fluorescence [37]. Reproduced with permission of Springer Nature

assessment as a marker for the development of diabetic complications [38]. The study lasted 5 years during which patients underwent measurement at least once a year. They found that skin autofluorescence was significantly associated with the development of neuropathy and (micro)albuminuria, but not with diabetic retinopathy (DR). In a further multi-center study, it was confirmed that skin autofluorescence is associated with the risk of micro- and macrovascular complications [151]. A study by Yasuda et al. evaluated the change in skin fluorescence in patients with DR [152]. They showed a gradual increase in this parameter during the development of retinopathy (from patients without complications to patients with nonproliferative and proliferative forms of retinopathy). Several studies have also shown an increase in the lifetime of AGE-associated fluorescence in the eyes, skin

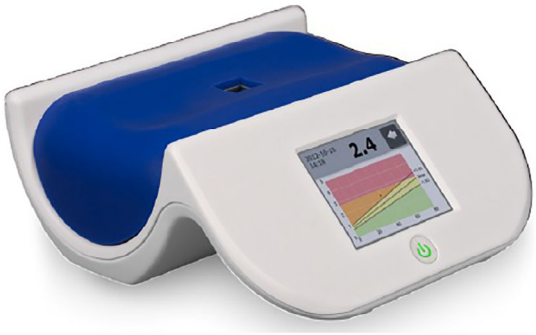


**FIGURE 7** AGE-Reader (DiagnOptics) [161]

and dentin of patients with diabetes [153–155]. In the studies, the authors use two- and three-term exponential fitting with the estimation of the parameters related to the time constant of fluorescence relaxation as well as the intensity of the corresponding fluorescent components. The gradual decrease in the average lifetime parameters of the first and second decay components with the increase of the AGEs has been demonstrated by the incubation of the collagen gel and dentin in ribose [39]. Remarkably, no significant differences in lifetime parameters were found in measurements on skin of diabetic patients and healthy volunteers [153], whereas an increase in cutaneous fluorescence is indicative of the development of diabetic ulcers [108, 156].

A substantial number of studies examined the applicability of AGE fluorescence in evaluating the risk of all-cause mortality and cardiovascular morbidity and mortality [157–159]. A recent review and meta-analysis indicated that elevated levels of AGE fluorescence could be a predictor of cardiovascular and all-cause mortality in patients with diabetes related cardiovascular and renal diseases [159]. This parameter was also demonstrated to effectively assess the 5-year risk of amputation in patients with PAD [160]. The widespread use of the AGE-level assessment in the diagnosis of DM complications and other diseases ultimately led to the successful commercialization of devices based on this technology. The first commercially available device was released by the Dutch company DiagnOptics, called the AGE-Reader. A photograph of the device is shown in Figure 7.

Although previous studies have shown a significant correlation of the skin autofluorescence level with the amount of collagen and AGEs [37, 162, 163], other fluorophores also contribute to the overall signal. The important components are the redox regulated fluorophores, NADH and FAD, which also exhibit autofluorescence. The redox status of tissues can be determined by assessing the fluorescence ratio of these coenzymes. This approach was applied in a study by Quinn et al., where the healing potential of diabetic wounds was evaluated in a diabetic mouse model [40]. Evaluation of the NADH/FAD ratio may have an important diagnostic value in the diagnosis of tissue oxygen metabolism disorder in DM [107]. Some studies have analyzed the difference in the AGE/NADH ratio between diabetics and healthy controls [164]. They reported a significant increase in this ratio among the former group.

## 2.6 | Optical coherence tomography

Optical coherence tomography (OCT) has found wide application in the diagnosis of DM complications. This technique is based on low-coherence interferometry and provides a cross-sectional image of the tissue studied. It can provide a two- or three-dimensional image of the tissue by measuring the echo delay and the intensity of the back reflected radiation (similar to the B-scan in ultrasonography). The method was developed in 1991 [165] and immediately became widespread in various medical applications, especially in ophthalmology.

OCT has been used in the diagnosis of DR and macular edema since the first commercial OCT scanners were introduced in 1995 [166]. Macular edema is a common cause of vision loss in diabetes, which can occur at any stage of the disease. The introduction of OCT in ophthalmology has dramatically improved the diagnosis of DR. Changes in the state of the retina and its blood supply can reflect a number of pathophysiological reactions to hypertension, inflammation, hyperglycemia, hypoxia and endothelial dysfunction, and thus can predict various microvascular complications of diabetes. At the beginning of the 1990s, the possibilities of diagnosing eye diseases using OCT were shown, and in a 1998 study, [42] OCT was used to evaluate macular thickening in patients with diabetes. Subsequent studies have confirmed the reproducibility of retinal thickening measurements using OCT [43].

In the studies conducted with time-domain OCT (TD-OCT), it was shown that patients with diabetes generally do not show differences in the retinal thickness compared with a healthy control group [167]. Concurrently, studies using spectral-domain OCT (SD-OCT) showed differences in the thickness of some layers of cells between diabetic patients without visible signs of DR and a healthy control group [44, 168]; in particular, the difference was observed for the layer of photoreceptors [45]. In addition, the dependence of this parameter on the duration of the disease [45] was demonstrated. A significant advantage of SD-OCT is that this method facilitates the analysis of a larger number of eye structures and the evaluation of the integrity of the outer layer of the retina.

SD-OCT was used to assess the choroidal thickness in patients with diabetic macular edema and various stages

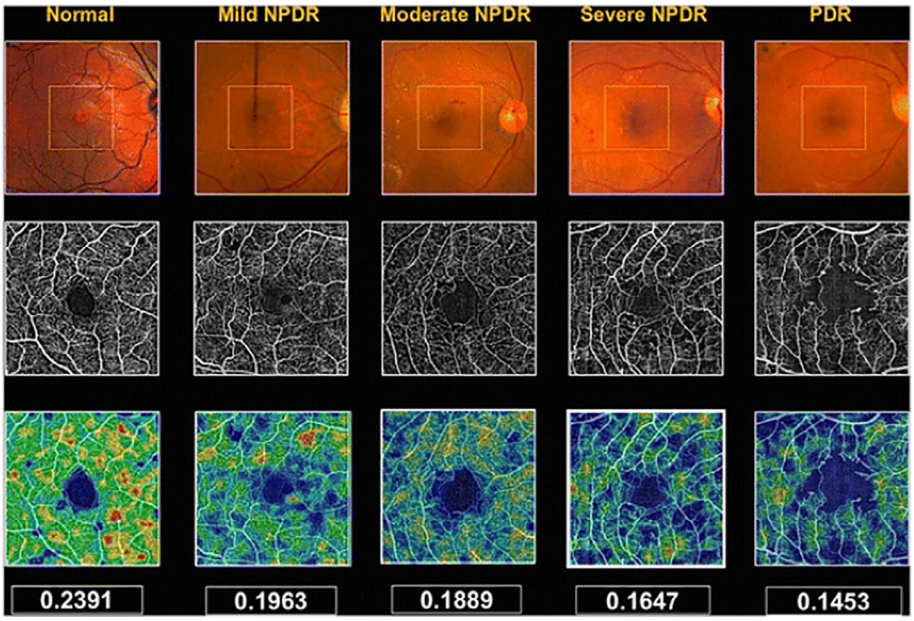



**FIGURE 8** Series of color fundus photos (top row), OCT angiograms (middle row), and color-coded vascular perfusion maps (lower row) demonstrating changes in perfusion density seen as diabetic retinopathy progresses [53] (NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy). Reproduced with permission of Springer Nature

of DR and a control group [46, 47], showing a decrease in this parameter in patients with diabetes, which may be one of the reasons for the development of eye disorders in this disease. The studies have been conducted on evaluating the effectiveness of macular edema treatments, demonstrating differences in the structure of the treated and untreated eye recorded by SD-OCT [166].

Recent investigations with advances in SD-OCT revealed significant changes in the nuclei and dendrites of retinal ganglion cells in patients with diabetes [48]. Surprisingly, a thinning of these structures was found not only among patients with advanced stages of DR, but also among those not showing signs of complications. More recent studies have linked changes in the structure of the retinal nerve tissues with the development of diabetic neuropathy, not retinopathy [49].

One of the promising directions in the diagnosis of microcirculation in ophthalmology is the use of optical coherence tomography angiography (OCTA). The method produces numerous B-scans of the retina, allowing visualization of the vascular system by recording changes in the intensity or phase of the OCT signal that appear as a result of blood movement. OCTA has been used to assess various retinal vascular changes that occur during the development of DM with or without DR [50–52], including microaneurysms, vascular loops, nonperfusion, neovascularization and foveal avascular zone erosion. Figure 8 presents the results of retinal perfusion measurements with OCTA of a control group and diabetic subjects with different stages of DR [53].

The OCT method is also widely used to assess wound healing. Several experiments have been conducted with laboratory animals [169, 170], as well as studies of burns [171–173]. However, similar studies of diabetic wounds were not identified.

Some studies were conducted on the estimation of the concentration of various substances using OCT, including the estimation of glucose and glycated hemoglobin in solutions and optical phantoms. The change in the optical properties of blood after the addition of glucose has been studied. The study of Galanzha and co-authors compared OCT measurements of different concentrations of glycated hemoglobin solutions in distilled water [56, 57].

In 2001, R. Esenaliev et al. demonstrated the ability of OCT to measure the concentration of blood glucose in phantoms and in animal models [54]. In their study, they compared the noninvasively measured OCT signal and glucometer data with a rapid glucose injection. They later confirmed that the results of measurements of the OCT curve slope correlate with measurements of blood sugar using a glucometer in the first clinical study performed on healthy volunteers [55].

## 2.7 | Confocal microscopy

The method of corneal confocal microscopy (CCM) is widely used in assessing eye changes between the healthy and diseased states [174, 175]. The technique allows the study of the corneal architecture under high magnification to evaluate the condition of the corneal nerves, for the diagnosis of DM complications. The principle is based on confocal optics, limiting the area of observation to a single point. In the study of the population of patients with diabetes using this technology, a correlation was

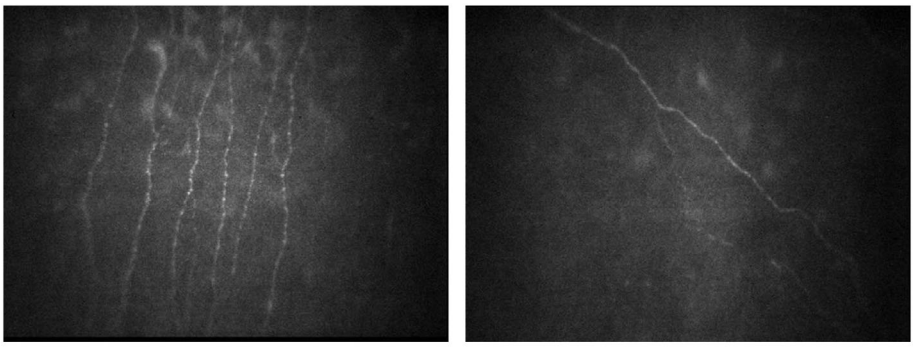



**FIGURE 9** Corneal confocal microscopy images obtained for: A, healthy volunteer (with typical beaded appearance, density, mild tortuosity, and adequate branching) and B, diabetic subjects with severe diabetic neuropathy showing single branch leaving main nerve trunk at bottom of frame [177]. Reproduced with permission of Elsevier

found between a decrease in the nerve fiber density and the severity of neuropathy [58]. In addition, it has been shown that diabetic nerve fibers are more tortuous, which is inversely correlated with the severity of diabetic neuropathy [59]. The authors believe that the tortuosity of the fibers can be associated with nerve regeneration and improved glycemic control [59, 175], similar to the previous animal studies [176]. Figure 9 presents CCM images of patients with varying degrees of diabetic neuropathy and a control group.

CCM was also used in recently diagnosed type 2 diabetes to detect early signs of neuropathy [60], showing greater sensitivity compared to the skin biopsy studies in some cases. The studies were conducted on changes in nervous corneal innervation during pancreas and kidney transplantations in patients with type 1 DM [61, 62]. A significant improvement in the density and length of the corneal nerve fibers was shown compared with the preoperative state. The authors conclude that CCM appears to represent a promising noninvasive and reiterative test with high sensitivity for assessing the benefits of pancreas transplantation and other therapies in clinical trials of human diabetic neuropathy.

## 2.8 | Raman spectroscopy

The Raman spectroscopy is based on inelastic scattering of monochromatic light by matter, which leads to energy transfer and molecular vibrations. The technique provides a highly specific probe with unique chemical fingerprinting of molecules. The method has found wide application in pharmacology, microbiology and human biology. A considerable number of studies have been done in oncology [178]. Traditional Raman spectroscopy has been used in the diabetic studies to assess the concentration of blood glucose in a sample [179]. Later, a noninvasive assessment of blood glucose concentration using Raman spectroscopy was carried out in an experiment on a mouse model [180]. The ability of the method to detect differences in the blood and serum of subjects with diabetes and healthy subjects based on the spectra of glucose, lipids, leucine and isoleucine amino acids was demonstrated [181, 182]. Thus, it has been shown that Raman spectroscopy can be a reliable method for diabetes screening in blood samples. It can also potentially be used to evaluate the effectiveness in diabetes therapy [181, 183].

The method has also been used to evaluate protein glycation in diabetes. For these purposes, numerous modifications of traditional Raman spectroscopy were used, including surface-enhanced Raman spectroscopy (SERS). In a study conducted by Kiran et al. [64], the possibility of using surface-enhanced resonance Raman spectroscopy (SERRS) to assess the accumulation of glycated hemoglobin, one of the most used markers for long-term glycemic control, was shown. In order to enhance the recorded Raman signal, the authors applied a solution of silver nanoparticles, after which they observed characteristic SERRS peaks in the range of 770 to 830 nm in HbA1c solution. It has also been proven that the peak at a wavelength of 827 nm originates from the glycated hemoglobin. The other study, conducted by Barman et al., applied drop coating deposition for quantification of HbA1c concentration in the whole blood [65].

The studies in the field of noninvasive assessment of AGE accumulation using Raman spectroscopy are of particular interest. In a study conducted by Paolillo et al., Raman and fluorescence techniques were simultaneously used [63]. In this study, the degradation of type I collagen and increased glycation was shown in diabetics and changes in the collagen hydration state was noted for diabetic and chronological aging groups, according to Raman spectroscopy data. The combination of fluorescence and Raman spectroscopy techniques was proposed for noninvasive diabetes diagnostics or diabetes risk prediction. Earlier works have already indicated the possibility of Raman spectroscopy to differentiate skin subjected to chronological changes or photoaging of young sun-protected skin [184]. Skin Raman spectra are shown in Figure 10.

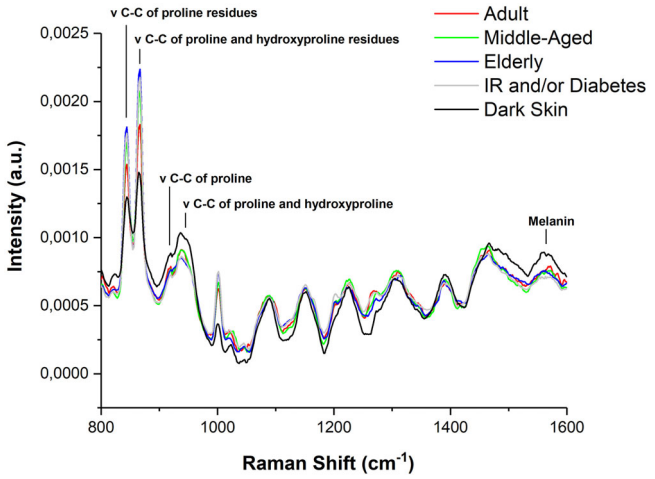



**FIGURE 10** Raman spectra of skin [63]. Reproduced with permission of John Wiley and Sons

In another study, performed by Guevara et al., a portable implementation of a Raman spectroscopy was used for the noninvasive screening of patients with type 2 diabetes [185]. Using machine learning and principal components analysis, the authors were able to discriminate between diabetic and control groups with an accuracy of 88.9% to 90.9%, depending on the measurement area.

Raman spectroscopy systems are usually equipped with CW lasers at an excitation wavelength of 532 or 785 nm.

## 2.9 | Terahertz

Terahertz pulsed spectroscopy and imaging utilize electromagnetic radiation in the frequency band from 0.1 to 10 THz (with wavelength 0.3-3 mm). This frequency range lies between the infrared and microwave ranges, and allows noninvasive diagnostics of biological tissues. THz imaging is highly sensitive to the water content of tissues, and therefore, it has found application in the fields of medicine related to the evaluation of biotissue hydration. It has been tested in skin, lung, breast and other types of cancer [186–188], as well as in assessing burn severity [189, 190] and wound healing [191].

Although this method has not yet been widely used to study the complications of diabetes, Hernandez-Cardoso et al have shown in their article that it has potential applicability in the diagnosis of diabetic foot syndrome [66]. Using THz reflection imaging, the study revealed a significantly reduced level of foot tissue hydration in patients with diabetes compared with healthy subjects and proposed this technique as a potential screening method for the early stages of diabetic foot syndrome. Figure 11 shows the THz images of the feet of control subjects and patients with DM.

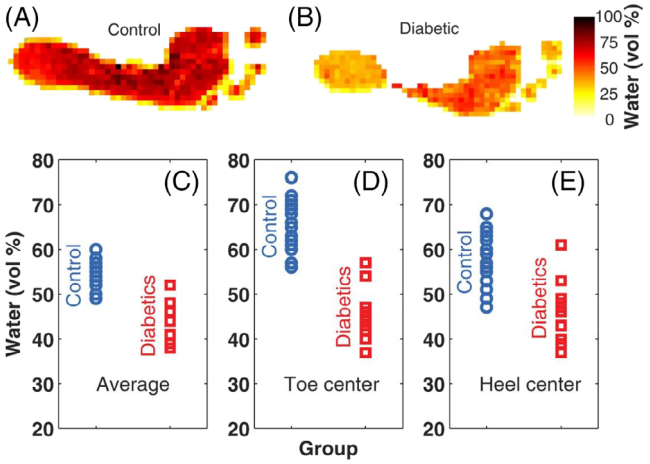



**FIGURE 11** Terahertz images of a typical member of the, A, control and, B, diabetic groups. Volumetric fraction of water for control and diabetic group members, C, averaged over the foot sole, D, at the center of the greater toe, and, E, at the center of the heel. Each point represents a subject [66]

## 2.10 | Other techniques

Other optical technologies that, although not yet widely adopted, have been used in the studies of DM and its complications are also worth mentioning.

A large number of the in vitro studies on changes in the optical properties of biological tissues under the influence of glycation were undertaken. Since our review is devoted to noninvasive methods for assessing disorders that occur during DM, we will not dwell on them in detail, and just list some. Using refractometry, the changes in the properties of red blood cells and hemoglobin solutions of patients with DM were evaluated [192, 193]. It has been proposed that these measurements be used to estimate the concentration of glycated hemoglobin.

In the studies of skin biopsy samples using atomic force microscopy (AFM), the changes in the mechanical properties of collagen in patients were shown compared with the control group [194]. The changes included a violation of the integrity of dermal collagen, disorganization of collagen fibrils, and nanoscale fragmentation. Figure 12 shows the nanoscale images of the skin morphology of a healthy subject and a patient with diabetes, as well as the mechanical properties of the skin.

Measurements of the glucose concentration in water solutions [195] and the accumulation of AGEs in pig skin samples subjected to glycation in a ribose solution [196] were conducted by optoacoustic spectroscopy. The authors claim that although optoacoustic methods have some drawbacks, such as the influence of the optical properties of the skin and their changes on the result, they have potential to overcome the limitations of purely optical spectroscopic methods.

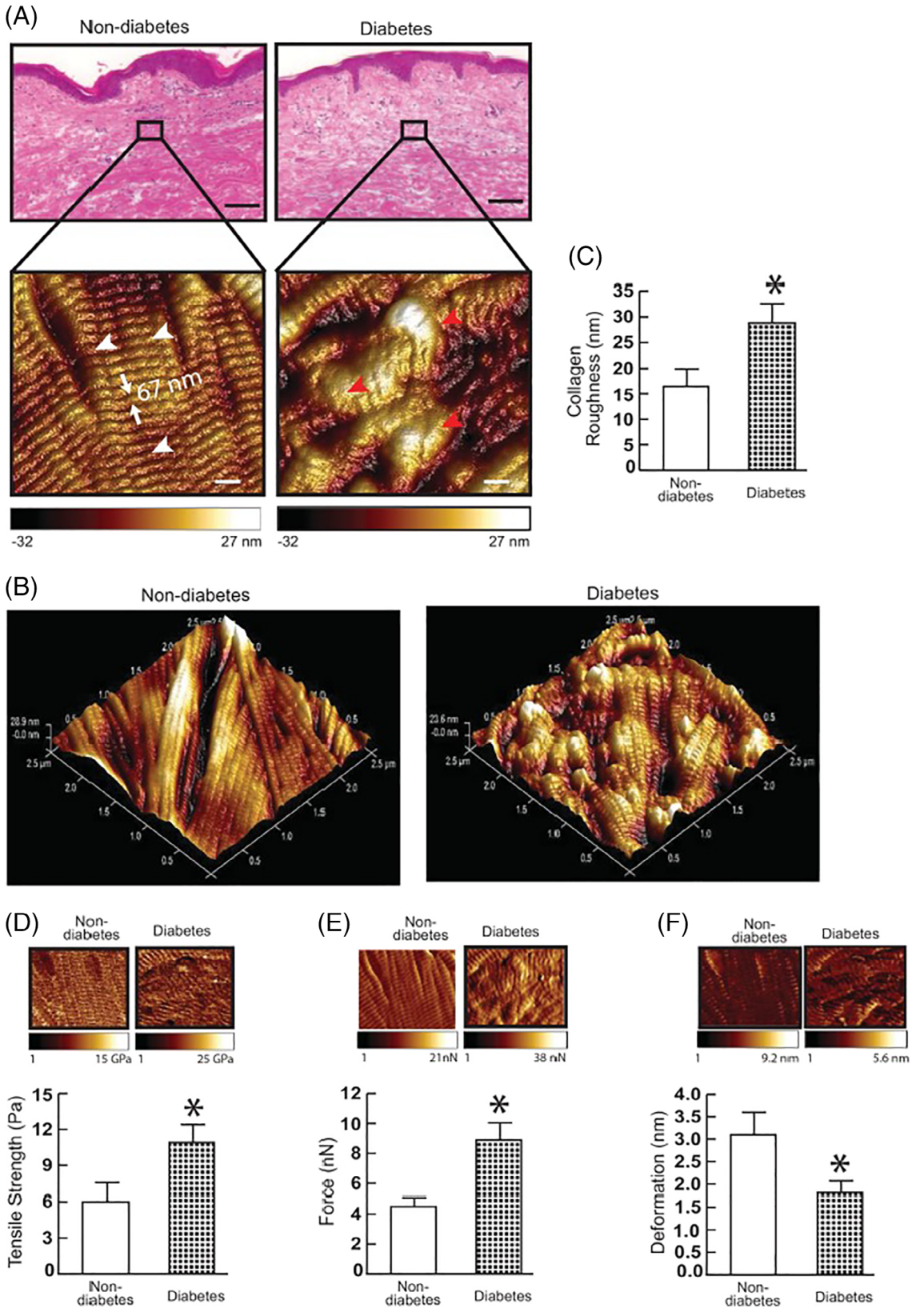



**FIGURE 12** Collagen fibril nanoscale morphology and mechanical properties of diabetic skin: A, Nanoscale collagen fibrils imaged by AFM. The white and red arrow heads indicate intact and fragmented/disorganized collagen fibrils, respectively. B, Three-dimensional nanoscale collagen fibrils imaged by AFM. C, Collagen fibril roughness analyzed using nanoscope analysis software, *$p < .05$. D, Tensile strength, E, traction forces, and F, deformation, *$p < .05$ [194]

Photoacoustic (optoacoustic) tomography (PAT) is widely used to analyze vascular disorders in PAD. Previous studies have shown the potential of technology in vascular imaging for a number of pathological changes, including oncology [197, 198], systemic sclerosis [199], disorders of cerebrovascular blood flow [200] and so on. Although the technology has already found wide application in the studies of vascular complications of various etiologies, it is little used in the studies of diabetes complications. At the moment, only a few examples of in vivo studies are conducted in the field of diabetes using PAT. In the work of Yang et al. [201] it was shown that PAT has a potential in the diagnosis of vascular function (on the example of changes arising from arterial and venous occlusion).

Diffusion optical tomography (DOT) was used in the studies of PAD [202, 203] and to assess the quality of diabetic ulcer healing [204]. The technique is based on sensing tissue with light of several wavelengths in the red and infrared ranges, followed by reconstructing two- and three-dimensional maps of tissue oxygenation and blood volume. The studies have shown that there are differences in changes in hemoglobin concentration in a healthy control group, patients with PAD, and a diabetic PAD cohort [203]. It is believed that DOT can significantly aid the diagnosis and treatment of diabetic foot disorders, providing information on the distribution of blood flow in the most compromised areas of the foot. The studies of diabetic ulcers in model animals using this technology showed significantly increased light absorption and scattering in the ulcer area in the diabetic group compared to the control group. An increasing trend in the absorption coefficient of diabetic ulcers during healing was shown, while in the control group, absorption remained almost constant throughout the healing process [204]. The authors associate such changes in diabetic animals with the process of the wound vascularization.

## 3 | CONCLUSIONS

Optical noninvasive diagnostic technologies are promising in the study of diabetes complications and have a large potential to aid clinical assessment. By using biophotonics methods, it is possible to assess the state of the microvasculature, monitor changes in tissue innervation and diagnose the effectiveness of diabetes therapy. Various spectroscopic and imaging techniques can evaluate parameters such as blood supply to tissues, degree of oxygen saturation, presence and concentration of various chromophores, and assess changes in the structure and functioning of different body systems.

In this review, we examined the use of various biophotonic methods. All of them can identify certain disorders that occur with diabetes, and seem promising in the field of early diagnosis and prevention of complications. However, most of these methods have not yet become widespread in clinical practice. Some technologies, such as OCT, are currently widely applied in certain areas of medicine, and further technical advances will increase the scope of its application. Other technologies, such as LDF, despite a significant scientific base, are not widely used in the clinic due to some methodological difficulties.

Recent advances in the optical noninvasive diagnosis of diabetes complications suggest a wider adoption of optical technology in clinical practice in the near future. We assume that such technologies as hyperspectral, fluorescence and speckle-contrast imaging are the closest to widespread implementation in clinical practice and can already be used in the work of the attending physician. Also, the combination of several biophotonics technologies for multiparametric diagnostics has great potential, but all the technologies described require further studies with thorough testing in the clinic. Finally, due to strong multiple scattering of light in biological tissues (especially skin) [7] optical imaging techniques are required to apply optical clearing agents to overcome a limitation associated with the narrow probing depth [205, 206].

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## CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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