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Continuous Blood Glucose Monitoring Using Non Invasive Technique: A Review

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***Abstract*—** *The advent of a pain free non-invasive technology would improve the patient's compliance for regular blood glucose monitoring. Subsequently the diabetic patient's life will improve considerably. Glucose monitoring is an integral part of diabetes management, and the maintenance of physiological blood glucose concentration is the only way for a diabetic to avoid life-threatening diabetic complications. Many reviews have already been published on this topic, but the great amount of information available and the fast development of technologies require a continuous update in the research status. This manuscript aims to review the various NGM techniques and devices.*

***Keywords*—** *Blood glucose monitoring, diabetes management, non – invasive technique.*

I. INTRODUCTION

Diabetes is one of the most prevalent and pressing diseases in the world today. It is caused by an insulin disorder that can be classified as type 1 or type 2 according to its underlying mechanism. Type 1 (also identified as insulin-dependent diabetes) results from an autoimmune attack destroying the insulin producing beta cells of the pancreas. Type 2 (also identified as non-insulin dependent diabetes) is a metabolic disorder characterized by high blood glucose involving insulin resistance and relative insulin deficiency. Additionally, high blood sugar levels during pregnancy cause a third type of diabetes, growth diabetes mellitus (GDM). Any kind of diabetes can be dangerous because long-term excess of glucose (hyperglycemia) can cause broken nerves, blindness and kidneys or even increase the risk of heart diseases, strokes, and birth defects. Low levels (hypoglycemia), however, can result in confusion, coma and even death.

Systems which puncture the skin are still standard techniques for home monitoring (6–7% accuracy) reading glucose concentrations through electrochemical, colorimetric or optical disposable strips for finger-prick blood samples [1]. Efforts have been made in order to reduce the level of invasiveness by decreasing the blood sample volume to a few micro litres, and measuring areas of the body less sensitive to pain than fingertips, such as the forearm, upper arm, or thigh. Drawbacks of such systems area lack of control during asleep or physical performance, undiscovered episodes of hyper- or hypoglycaemia, risks of illness, nerve damage and the discomfort of pricking the finger several times a day, which painful activity often leads to non-compliance. Minimally invasive measurements sample the interstitial fluid with subcutaneous sensors. Even in this method the discomfort causes difficulties to the patient's therapy. Therefore, research crowds are working to build up non-invasive glucose control devices [2]. Unfortunately, so far there are no reports or patents which show that such non-invasive methods have the same precision as invasive measures. Although there are many complete reviews of painless blood glucose techniques [3-5], the great volume of recent research results in this field requires a constant update. Therefore, besides the explanation of vital measurement approaches, this work also shows on hand devices in the market with their technologies and measurement places. Because absorption spectroscopy is a usual sensing method, the wavelengths used in non-invasive tests will also be explained. In addition, algorithms for multivariate investigation will be presented, showing that current improvements in technologies and multi parameter measurements may still make possible improved accuracy of the predictions.

II. NON–INVASIVE GLUCOSE MONITORING

Non-invasive technique is mostly depends on absorption or transmittance. Blood glucose gives dissimilar absorption spectrum for dissimilar wavelengths. One option to painless alternating glucose control is the replacement of blood with other fluids that could contain glucose, like saliva, urine, sweat or tears.

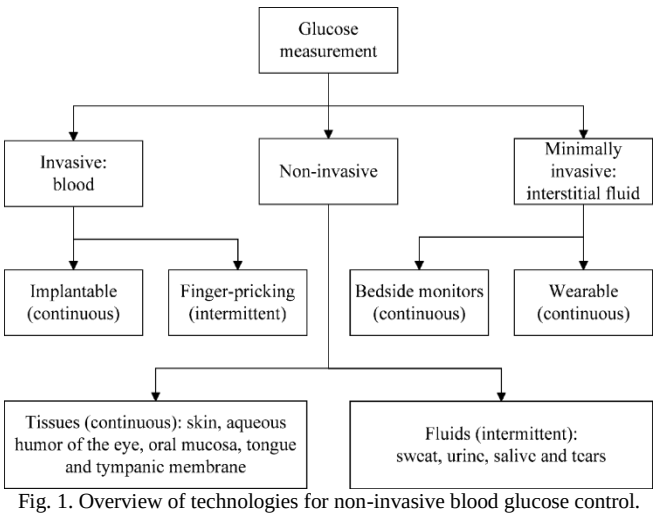

Fig. 1. Overview of technologies for non-invasive blood glucose control.

Non-invasive analysis have been already published using technologies like reverse iontophoresis, Raman, light absorption, polarimetry, ultrasound, metabolic heat conformation, thermal emission, electromagnetic, photo acoustic and Bioimpedance spectroscopy. Together with the choice of technique and sample region, one should also give

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attention to parameters of the measurement surroundings. For instance, in the case of transdermal monitoring, ambient temperature, skin colour, tissue thickness, surface roughness, breathing artifacts, blood flow, sweating, body movements, pressure and sample duration also influence the results.

A. *Infrared Spectroscopy*

The Infrared Spectroscopy make use of both the absorption & scattering phenomenon of the light when focussed over the trial tissues for analytical point. The light and trial tissue interactions produce molecular specific pulsation information of the absorption and scattering occurrence in the infrared spectral domain.

When light meets biological tissues it can undergo reflection, scattering and transmission being proportional to the configuration and chemical apparatus of the sample. The prospect of molecular differentiation is, therefore, the reason why the mainstreams of continuous glycemic monitoring efforts are focused in the optical mark spectrum of glucose.

Fig. 2. Glucose monitoring using infrared spectroscopy.

Many spectroscopic analysis have been done in noticeable and near infrared (NIR) range, namely around 590–950nm [6], 1212–1850nm [7–9] and 2120–2380nm [10]. Such spectra are chosen since water absorbance is weak, the measuring signal has high energy and there is a wide number of commercial light transducers available. These wavelengths are establish in the therapeutic window (600–2500nm) allowing the use of reflectance for superficial layers investigation and transmittance in deep tissues measurements [11].

On the other hand, the use of middle infrared (MIR) spectra (mostly between 8382nm and 9708nm) [12–14] gives more distinctive glucose peaks. However, unluckily these spectra have restricted light penetration, excluding use in transmittance checking. A substitute to increasing optic penetration is the dimension with attenuated total reflection (ATR) [15], which uses a light beam direct through a crystal by total reflection. If the crystal surface is located in contact with the skin, the electromagnetic field formed by the reflected light reaches the dermis, where the interstitial fluid includes most of the skin glucose. Therefore, alters in the beam absorption should reflect the optics features from blood sugar. The use of squalling oil in the crystal interface seems to improve quantitative prediction.

B. *Reverse Iontophoresis*

The method of iontophoresis has been utilized for many decades and makes use of electrical current to deliver exciting drug compounds throughout the skin. Non-invasive monitoring, however, uses transfer of glucose in the opposite direction that of normal medicaments, therefore this process has been called reverse iontophoresis [16]. The GlucoWatch is a wrist-watch glucose control device manufactured by Animas Technologies that make use of such techniques with two independent potentio state circuits [17]. This measurement is probable because neutral molecules, such as glucose, are extracted through the epidermis surface via this electro-osmotic flow to the iontophoretic cathode, along with Na^+ ions.

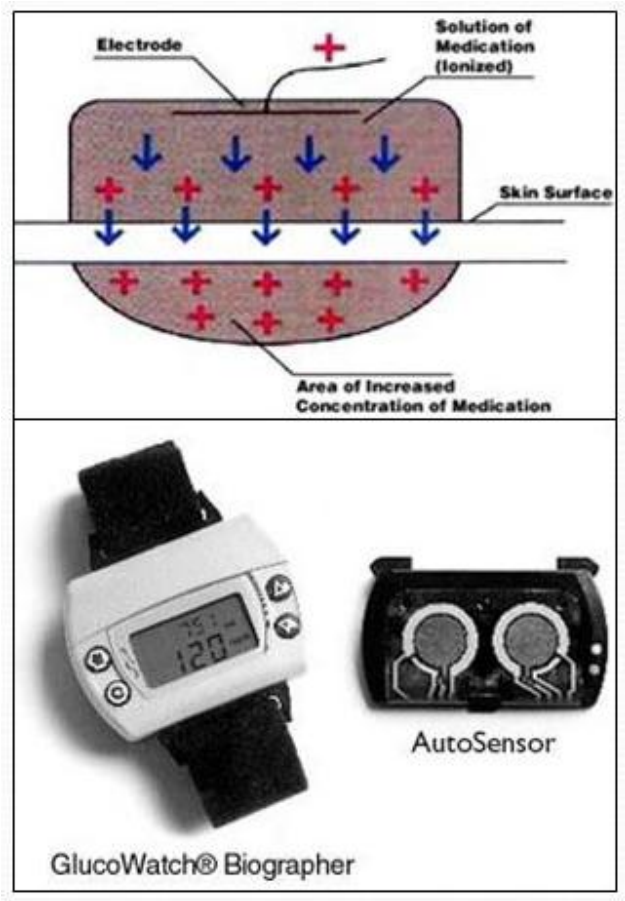

Fig. 3. Glucose monitoring using reverse iontophoresis.

Glucose concentrations pull out through the skin with mA currents are in M ranges; therefore, the ampere metric circuit wants to detect glucose from 50pmol to 200pmol. In this electrode, blood sugar is serene in hydrogel discs containing the enzyme glucose oxidase (GOx). These hydrogels, which want to be often replaced, comprise the electrolyte of an amperometric biosensor, working with nA currents to perceive H_2O_2 generated by the glucose oxidase-catalyzed reaction. After the solute taking out and measurement phases, mathematical algorithms calculate glucose level in the display. This processing not only uses the biosensor reaction, but also skin temperature and perspiration fluctuations, through thermo transducers and conductivity sensors obtainable in the device. The system is able to read glucose values every 10min for up

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to 13h. Correlation coefficients between biographer and finger-stick measurements are about 0.865, although the approval by U.S. Food and Drug Administration (FDA) for an auxiliary method, without replacing invasive control, such a device is no longer available due to its inadequate performance. Some disadvantages of the technology contain the time delay compared with blood values, inaccuracies of results, skin irritation, long calibration procedures and a 2–3h warm-up period [18, 19]. Another reverse iontophoresis device available is the GluCall from KMH Company, which needs 70min to warm up and measures glucose values every 20min for up to 6 h.

C. Raman Spectroscopy

The process where a small part of scattered light shows wavelengths dissimilar from that of the exciting beam is known as the Raman Effect. This type of spectroscopy uses laser radiation sources from noticeable to the MIR range and measures very weak signals in the visible samples. The measured photons normally have upper wavelength and lesser intensity (10^{-3} times) than the original light, therefore requiring longer collection periods than other optical methods [20].

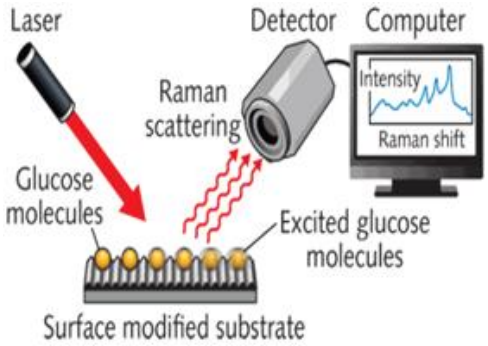

Fig. 4. Glucose monitoring using raman spectroscopy.

Water has weak scattering indexes, which is the reason why the Raman evaluates are not affected by interference from this substance. Another advantage is that the resulting bands are narrow and have distinct peaks, easing the task of separating signals, in contrast to absorption spectroscopy [21]. A recent study reports measurements of glucose in aqueous humour with a 785nm laser source. An optical fibre was used to focus the beam on the anterior chamber of porcine eyes and also to receive the resulting spectrum. Results suggest that Raman signals from glucose in MIR range can be detect able with this system. Nevertheless, one should still analyse photo thermal damage danger in non-invasive ocular measurements before addressing human tests.

D. Fluorescence

It is known that glucose levels in tears reflect concentrations similar to those in blood. Therefore, fluorescence is also a sensing technology to painless monitoring [22]. This system can follow blood glucose with an approximate 30 min lag time and does not suffer interference from fluctuations in the light intensity of the ambient surrounding. The photonic sensing is done with polymerized crystalline colloidal arrays which react to different concentrations through diffraction of visible light.

Fig. 5. Glucose monitoring using fluorescence.

The sensor can be disposable colourless contact lenses, requiring excitation and detection devices. Recent results of in-vivo test with such transparent lenses excited in 488 nm showed results correlate with control glucose levels. On the other hand, long-term studies of comfort and toxicity still need to be performed. Extra equipment could be discarded through the use of coloured contact lenses. By changing colour in response to the concentration of glucose in the tears, patients could look into a mirror and compare the sensor colour to a recalibrated colour strip. Some restrictions still need to be solved in colorimetric tests, such as short life times resolution and biocompatibility.

E. Photoacoustic Spectroscopy

Photoacoustic spectroscopy (PAS) is based on ultrasonic waves formed by tissue absorption of pulsating light [23]. When laser beams meet cells, heat is produced, causing pressure variations in the sample. These acoustic signals can be detected throughout a piezoelectric transducer, and with the specific incident wavelengths reflect optical properties of glucose in blood [24]. PAS non-invasive glycemic monitoring devices, like the Aprise from the Glucon company, are previously available in the market. Although this method was shown to link with blood sugar levels, it is still essential to improve the reproducibility and sensitivity in order to reduce interferences from other substances.

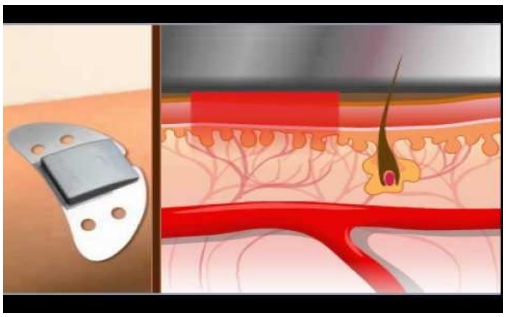

Fig. 6. Glucose monitoring using photoacoustic spectroscopy.

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F. Bioimpedance Spectroscopy

The first swot of non-invasive continuous glucose monitoring system involving impedance spectroscopy was published by Caduff's group in 2003. As result from this research, the company Pendragon developed a wrist glucose monitor called Pendra. The apparatus collects information of a LC resonance circuit from 1MHz until 200MHz, with the skin working as dielectric from the capacitor. One constraint of this research is that it needs an equilibration process, where the patient must rest for 60 min before starting measurements [25].

Fig. 7. Glucose monitoring using bioimpedance spectroscopy.

Pendra was approved in May 2003 in the Conformite´ Europeenne´ (CE) and for a short time it was presented on the market for approximately D 3000. A post-marketing consistency study showed a distinction of 52% (4.3% of the readings in the dangerous zone E from Clarke error grid) when balanced with a lancet device [26]. Therefore, this apparatus is fit only for a small group of customers, whose local dielectric skin characteristics show a minimum resonance frequency. In 2005 Pendragon was closed, but Caduff's impedance work has still been scrutinized through the company Solianis Monitoring.

G. Thermal Emission Spectroscopy

Thermal emission spectroscopy measures IR signals produced in the human body as a result of glucose concentration changes. One promising application of this technology uses related concept as standard clinical tympanic crust thermometers, with the addition of specific wavelengths for glucose finger print (9.8m and 10.9m). This membrane information is important, because it shares the blood supply with the middle of temperature regulation in the hypothalamus. In addition, signals from blood vessels in this organ have to cross a slighter path length than in skin or oral mucosa spots. A prototype was standardized and experienced in patients demonstrating reproducibility and predicting glucose concentrations with a signify error of 0.638mmol/L [27]. Body movements and ambient temperature are the most important sources of noise in such approach.

H. Ultrasound

Reverse iontophoresis is not the only technique of extracting non-invasive glucose molecules from skin. Sonophoresis, which generally improves transdermal delivery of drugs, can also serve this purpose [28]. This technique uses a piezoelectric transducer to generate 20kHz ultrasound (US) that increases cutaneous permittivity to interstitial fluid, enabling glucose to be transported to the epidermis surface. Analytic concentrations can therefore be determined with benchmark electrochemical glucose sensors. Initial in-vivo laboratory results have been described predicting glycemic values in rat skins throughout US.

Fig. 8. Glucose monitoring using GlucoTrack DF-F.

I. Metabolic Heat Conformation

The metabolic heat conformation (MHC) technique involves measurements of physiologic indices correlated to thermal generation, blood flow rate, hemoglobin, and oxyhemoglobin concentrations, which should match to the glucose levels in the blood [29]. Since such a technique can suffer strong interference of environmental conditions, it is predominantly used as auxiliary data to glucose quantification.

Fig. 9. Metabolic heat conformation blood sugar monitoring device from Hitachi.

The initial checks used three different temperature measurements (background radiation, surface finger and ambient room) derived from the fingertip during 10s. In addition, multi wavelength spectroscopy with six wavelengths (470nm, 535nm, 660nm, 810nm, 880nm, and 950nm) was performed, helping to get better glucose signals. The first MHC trial product, shown in Fig. 9, has a correspondence coefficient of 0.91 in laboratory conditions, but the company Hitachi intends to advance its performance in order to obtain sale support.

J. Electromagnetic

Electromagnetic sensors based on Eddy currents have been able to identify variation of the dielectric parameters of the blood, which can also be caused by glucose concentration changes [30]. Conductivity discovery of blood inside a plastic tube was probable at a resonant frequency of 2.664 MHz in static and moving samples, showing a glycemic sensitivity of

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4.4mmol/L [31]. Studies from Oz¨ group can also be explained in magnetic glucose tests. This work accounted that even localized nuclear magnetic resonance (NMR) has shown good performance to identify glycogen metabolism in the human brain.

Fig. 10. Glucose monitoring using electromagnetic sensor.

III. CONCLUSIONS

An increase of the signal-to-noise ratio is still required for all non-invasive tests. This should be skilled with a new generation of transducers and techniques. The similar monitoring of more than one parameter must also assist to enrich sensitivity. Primary studies have already been reported with concurrent monitoring of bioimpedance and near-infrared spectroscopy in the skin. The Glucotrack device from the company Integrity Applications is a industrial multi parameter monitoring device, where glucose is envisaged with conductivity, ultrasound and heat capacity.

In the controlled conditions of research laboratories it is relatively easy to measure data and find connection with blood glucose levels. The challenge is to found stable calibration models which are capable to measure in the normal circumstances of a patient's life. At last, the new production of bloodless glucose devices should have technologies to remove interfering species and competing biochemical pathways with accuracy, fast response, low cost and simple calibration procedures, recuperating the comfort of patients and also avoiding long-term difficulties.

IV. FUTURE SCOPE

This Continuous Glucose Monitoring is also reviewing the recent and upcoming nano material-based skills utilizing sweat, breath, saliva and tears as a diagnostic medium for diabetes monitoring.

REFERENCES

[1] D. C. Klonoff, "Continuous glucose monitoring: road map for 21st. century diabetes therapy," *Diabetes Care*, vol. 28, issue 5, pp. 1231–1239, 2005.
[2] J. C. Pickup, F. Hussain, N. D. Evans, and N. Sachedina, "In vivo glucose monitoring: the clinical reality and the promise," *Biosens Bioelectron*, vol. 20, issue 10, pp. 1897–902, 2005.
[3] T. Koschinsky and L. Heinemann, "Sensors for glucose monitoring: technical and clinical aspects," *Diabetes/Metabolism Research and Reviews*, vol. 17, issue 2, pp. 113–123, 2001.
[4] A. Tura, A. Maran, and G. Pacini, "Non-invasive glucose monitoring: assessment of technologies and devices according to quantitative criteria," *Diabetes Research and Clinical Practice*, vol. 77, issue 1, pp.16-40, 2007.
[5] A. Sieg, R. H. Guy, and M. B. Delgado-Charro, "Noninvasive and minimally invasive methods for transdermal glucose monitoring," *Diabetes Technology & Therapeutics*, vol. 7, issue 1, pp. 174–97, 2005.
[6] O. S. Khalil, "Non-invasive glucose measurement technologies: an update from 1999 to the dawn of the new millennium," *Diabetes Technology & Therapeutics*, vol. 6, issue 5, pp. 660–697, 2004.
[7] B. Leboulanger, R. H. Guy, and M. B. Delgado-Charro, "Reverse iontophoresis for non-invasive transdermal monitoring," *Physiological Measurement*, vol. 25, issue 3, pp. R35–50, 2004.
[8] R. O. Potts, J. A. Tamada, and M. J. Tierney, "Glucose monitoring by reverse iontophoresis," *Diabetes/Metabolism Research and Reviews*, vol. 18, issue 1, pp. S49–53, 2002.
[9] R. Panchagula, O. Pillai, V. B. Nair, and P. Ramarao, "Transdermal iontophoresis revisited," *Current Opinion in Chemical Biology*, vol. 4, issue 4, pp. 468–473, 2000.
[10] H. D. Park, K. J. Lee, H. R .Yoon, and H. H. Namb, "Design of a portable urine glucose monitoring system for health care," *Computers in Biologyand Medicine*, vol. 35, issue 4, pp. 275–286, 2005.
[11] S. J. Yeh, C. F. Hanna, and O. S. Khalil, "Monitoring blood glucose changes in cutaneous tissue by temperature-modulated localized reflectance measurements," *Clinical Chemistry*, vol. 49, pp. 924–34, 2003.
[12] K. Maruo, M. Tsurugi, J. Chin, T. Ota, H. Arimoto, and Y. Yamada, "Noninvasive blood glucose assay using a newly developed nearinfrared system," *IEEE J Selected Top Quantum Electron*, vol. 9, pp. 322–330, 2003.
[13] W. Schrader, P. Meuer, J. Popp, W. Kiefer, J. U. Menzebach, and B. Schrader, "Non-invasive glucose determination in the human eye," *Journal of Molecular Structure*, vol. 735–736, pp. 299–306, 2005.
[14] S. Kasemsumran, Y. Du, K. Maruo, and Y. Ozaki, "Improvement of partial least squares models for in vitro and in vivo glucose quantifications by using near-infrared spectroscopy and searching combination moving window partial least squares," *Chemometrics and Intelligent Laboratory Systems*, vol. 82, pp. 97–103, 2006.
[15] J. T. Olesberg, L. Liu, V. Van Zee, and V. A. Arnold, "In vivo near-infrared spectroscopy of rat skin tissue with varying blood glucose levels," *Proceedings of the SPIE*, 5325, pp. 11–20, 2004.
[16] J. G. Webster, Design of Pulse Oximeters, Philadelphia: Institute of Physics publishing Ltd., pp. 86–96 (chapter 7), 1997.
[17] C. D. Malchoff, K. Shoukri, J. I. Landau, and J. M. Buchert, "A. novel noninvasive blood glucose monitor," *Diabetes Care*, vol. 25, issue 12, pp. 2268–2275, 2002.
[18] W. B. Martin, S. Mirov, and R. Venugopalan, "Using two discrete frequencies with in the middle infrared to quantitatively determine glucose in serum," *Journal of Biomedical Optics*, vol. 7, issue 4, pp. 613–618, 2002.
[19] Y. C. Shen, A. G. Davies, E. H. Linfield, T. S. Elsey, P. F. Taday, and D. D. Arnone, "The use of Fourier-transform infrared spectroscopy for the quantitative determination of glucose concentration in whole blood," *Physics in Medicine and Biology*, vol. 48, issue 13, pp. 2023–2032, 2003.
[20] L. M. Harvey and B. McNeil, "At-line monitoring of ammonium, glucose, methyl oleate and biomass in a complex antibiotic fermentation process using attenuated total reflectance-mid-infrared (ATR-MIR) spectroscopy," *Analytica Chimica Acta*, vol. 561, issue 1-2, pp. 218–224, 2006.
[21] Y. Wickramasinghe, Y. Yang, and S. A. Spencer, "Current problems and potential techniques in in-vivo glucose monitoring," *Journal of Fluorescence*, vol. 14, issue 5, pp. 513–520, 2014.
[22] T. J. Allen, B. T. Cox, and P. C. Beard, "Generating photoacoustic signals using high peak power laser diodes," *Proceedings of the SPIE*, vol. 5697, San Jose, USA, pp. 233–242, 2005.
[23] O.K. Cho, Y.O. Kim, H. Mitsumaki, and K. Kuwa, "Noninvasive measurement of glucose by metabolic heat conformation method," *Clinical chemistry*, vol. 50, issue 10, pp. 1894–1898, 2004.
[24] C. D. Malchoff, K. Shoukri, J. I. Landau, and J. M. Buchert, "A novel noninvasive blood glucose monitor," *Diabetes Care*, vol. 25, issue 12, pp. 2268–2275, 2002.
[25] A. Caduff, E. Hirt, Y. Feldman, Z. Ali, and L. Heinemann, "First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system," *Biosensors and Bioelectronics*, vol. 19, issue 3, pp. 209–217, 2003.

[26] I. M. E. Wentholt, J. B. L. Hoekstra, A. Zwart, and J. H. DeVries, "Pendra goes Dutch: lessons for the CE mark in Europe," *Diabetologia*, vol. 48, issue 6, pp. 1055–1058, 2005.

[27] J. Kost, S. Mitragotri, R.A. Gabbay, M. Pishko, R. Langer, "Transdermal monitoring of glucose and other analytes using ultrasound," *Nature Medicine*, vol. 6, pp. 347–350, 2000.

[28] S. M. Alavi, M. Gourzi, A. Rouane, and M. Nadi, "An original method for noninvasive glucose measurement: Preliminary results," *Proceedings of the 23rd Annual International Conference of the IEEE*, Istanbul, 2001, vol. 4, pp. 3318–3320, 2001.

[29] M. Gourzi, A. Rouane, R. Guelaz, M. S. Alavi, M. B. McHugh, and M. Nadi, "Non-invasive glycaemia blood measurements by electromagnetic sensor: Study in static and dynamic blood circulation," *Journal of Medical Engineering & Technology*, vol. 29, issue 1, pp. 22–26, 2005.

[30] F. M. Ham, G. M. Cohen, I. Kostanic, and B. R. Gooch, "Multivariate determination of glucose concentrations from optimally filtered frequency warped NIR spectra of human blood serum," *Physiological Measurement*, vol. 17, issue 1, pp. 1–20, 1996.

[31] K. Yamakoshi and Y. Yamakoshi, "Pulse glucometry: A new approach for noninvasive blood glucose measurement using instantaneous differential near-infrared spectrophotometry," *Journal of Biomedical Optics*, vol. 11, issue 5, pp. 054028, 2006.