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Non-Invasive Measurement of Blood Glucose Biomimetics with the Reflectance Method on Near-Infrared Light Source

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Abstract. The non-invasive glucose biomarker device is developing to compensate for the epidemiology of sufferers of metabolic syndrome in the world from increase dramatically. Additionally, to eliminate all risks arising from the invasive measurement. The percentage of population sufferers of glucose metabolic syndrome evenly occurs in each developing and developed country. All individual activities and behaviors are the main causes. The device was conducted at the Electronic and Material Physics Laboratory, IPB University. This study used Assayed Chemistry Clinical Control as a sample, UV-cuvettes as a simulation tool, and a probe from a silk-polylactic acid filament. The incident light source biomarker uses near-infrared (NIR) LED 1200 nm, LED 1300 nm, and FDG03-Ge as a photodetector. Data analysis derived from reflectance values in the form of intensities expanded using Discrete Fourier Transform (DFT). The output analysis of both LEDs was 0.99 pearson, 100% clinical accuracy, and the accuracy of measurement was 8.09 mg/dL on the 1200 nm LED, 10.57 mg/dL on the 1300 nm LED. Then the sensitivity value of both LEDs is 1.00, and the specificity of 1200 nm LED is 0.80, LED 1300 nm is 0.70. Refers to the results of this analysis and the gold standard ISO 15197, LED 1200 nm is an ideal candidate for the incident light source biomarker non-invasive reflectance method. Future research expected to do device testing in-vivo.

INTRODUCTION

The epidemiology of patients with impaired glucose metabolism syndrome (Mets) is steadily rising in the world and all regions. Glucose Mets are a significant health case that reaches alarming levels in 2019; half the population from all over the world lives with impaired glucose metabolism [1]. Information on glucose Mets sufferers from International Diabetes Federation (IDF) in the world in 2019. There are 463 million and is expected to increase by

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51% to 2045. Africa in 2019 is 19 million and increase 143% until 2045, South and Central America in 2019 is 32 million and increase 55% to 2045, North America and the Caribbean in 2019 there were 48 million and an increase of 33% until 2045 [2].

Increases in patients with glucose Mets are influenced by lifestyle factors [3], diet [4], sleep patterns [5], consumption of drugs [6], physical activity [7], genetic [8], environment and psychology [9], 10], family history [11] and socio-economic [12,13]. If the individual has suffered from glucose Mets, glucose-related diseases will attack. Glucose Mets diseases are diabetes, monogenic, exocrine, and endocrine pancreas. Parameter diagnosis values in plasma glucose >7.0 mmol/L and Hba1c > 48 mmol/mol [1,14].

The symptoms and effects of glucose Mets slowly affect the productivity, socio-economy, and quality of life of each individual [1]. Glucose Mets are very progressive and challenging to classify, so it needs new control in the form of routine to checks [2,14]. This time, in various method devices of the world, is invasive and non-invasive. Invasive methods have a risk of transmission of disease, infection, physical trauma, and biological waste, unlike the case with non-invasive methods that can eliminate these problems [15]. Non-invasive methods are an ideal choice for blood glucose monitoring. The behavior of individuals and glucose Mets epidemiological in the current era is the researcher's purpose for developing non-invasive biomarkers. Specifically, this research is aimed at finding LED as light sources in the range of the NIR. Then compare it with other methods and whether the reflectance method can use as a non-invasive biomarker device.

METHOD

This experiment was conducted at the Laboratory of Electronics and Material Physics, IPB University, from September 2019 to January 2020. The circuit of biomarkers used in this study is the development of a variety of previous research references, which are then simplified [16].

In-vitro research begins by printing a probe design for setting a light source and detector. Incident light sources used are light-emitting diode (LED) 1200 nm and 1300 nm and FDG03-Ge Photodiode detectors [17,18]. Next is the sample or Reference Glucose Concentration (RGC) preparation of the Assayed Chemistry Clinical Control from the Bio-Rad Laboratory. The glucose concentration sample is divided into levels 1 - 87.3 (77.5-97.1) mg/dL and levels 2 - 278 (255-301) mg/dL in a 12 x 5 mL bottle size. Level 1 use as sample 1, level 2 use as sample 2, and a mixture of combinations between levels 1 and 2 used as sample 3 [19].

The measurement cuvette used is an ultra-micro transparent UV-cuvettes from quartz material [20]. The sample is put into a cuvette using a pipette. Then the cuvette is inserted into a probe that printed from a user-friendly 3D printer filament. Measurement process using SQ Lite to set up menu and Discrete Fourier Transform (DFT) to widening the data from intensity [16,21,22]. From these Pearson were obtained for each LED in periods 1-40. Next processing uses Error Grid Analysis (EGA) and Analysis of Epidemiological Data (epiR) to determine the accuracy, sensitivity, and specificity of the LED [23,24].

RESULTS AND DISCUSSION

Analysis of Discrete Fourier Transform

Statistical analysis uses the ZunZun server on the expansion of sample data from DFT. Each LED has a value of Root Mean Square Error (RMSE) of 8.09 mg/dL at LED 1200 nm and 10.57 mg/dL at 1300 nm. When referring to the ISO 15197 gold standard, the 1300 nm LED is automatically eliminating. The predetermined gold standard value is 10.00 mg/dL [25,26].

Error Grid Analysis

The risk of prediction errors of the value of a glucose level is comparing the predicted value of a non-invasive biomarker with the average value of the Assayed Chemistry Clinical Control. Both values are plot using the Clarke Error Analysis (CEG) and Parkes Error Analysis (PEG). Error analysis calculations show a score of 100% A from the 15 predicted data on the two LEDs (Fig. 1). The plot in zone factor A represents that both LEDs have an accuracy of measurement without error.

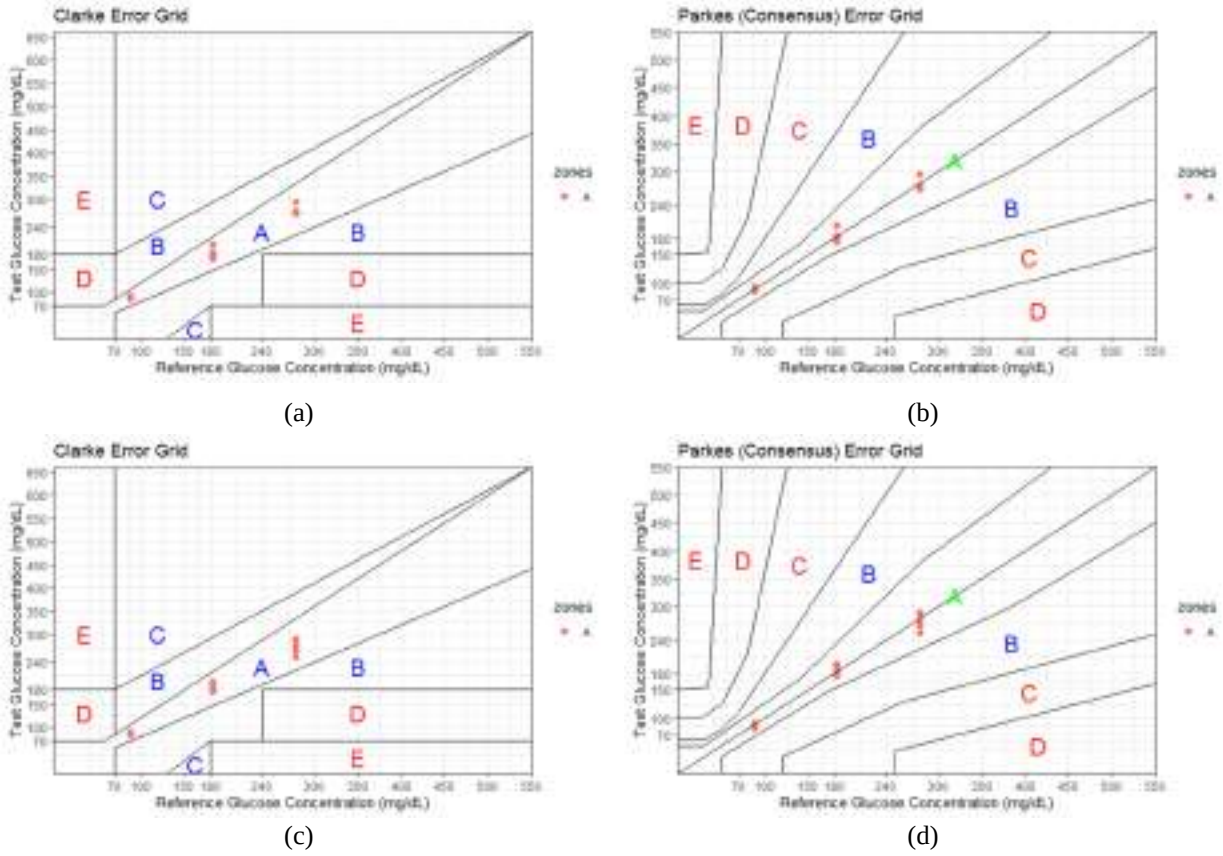

FIGURE 1. The results of the analysis of PEG using RStudio between Test Glucose Concentration (TGC) mg/dL and Reference Glucose Concentration (RGC) mg/dL with the wavelength LEDs, a) 1050 nm, b) 1070 nm, c) 1085 nm, d) 1445 nm, e) 1550 nm.

The CEG output values of the two LEDs show better than with the Scattering Spectroscopy (zone factor A 65.9%, zone factor B 34.1%), Rayleigh Theory (zone factor A 72.2%, zone factor B 27.3%), Orsense NBM devices (zone factor A 69.7%, zone factor B 25.7%) and Joint Electrical-Optical devices (zone factor A 77.86%, zone factor B 22.14%) [27]. A good response has shown in similar non-invasive biomarker measurements in the reflectance method, which test on patients with an incident light source of 800-2500 nm [28].

Analysis of Epidemiological Data

Calculation of epiR on the comparison of predictive TGC with REF through the division of two groups of each data with a median of 15 real data. The next calculation process uses the epiR library and RStudio software (Table 1). The point estimate values for the two LEDs are not much different. However, the 1200 nm LED is excellent compared to the estimated value of the 1300 nm LED.

The estimated sensitivity and specificity points of the non-invasive biomarker device reflectance method have qualified means of 1.00 and 0.80 when compared to other non-invasive methods. Non-invasive optical measurement method estimation points sensitivity 0.83, specificity 0.90 [16], glucose area under the curve (AUC) monitoring system sensitivity 0.82, specificity 0.88 [29] and clinical accuracy assessment algorithm sensitivity 0.95, specificity 0.96 [30].

TABLE 1. Poin estimates of analysis of epidemiological data

Characteristics	Light Source of Non-Invasive Biomarker Device	
	LED 1200 nm	**LED 1300 nm**
Apparent prevalence	0.47 (0.21, 0.73)	0.53 (0.27, 0.97)
True prevalence	0.33 (0.12, 0.62)	0.33 (0.12, 0.62)
Sensitivity	1.00 (0.48, 1.00)	1.00 (0.48, 1.00)
Spesificity	0.80 (0.44, 0.97)	0.70 (0.35, 0.93)
Positive predicted value	0.71 (0.29, 0.96)	0.62 (0.24, 0.91)
Negative predicted value	1.00 (0.63, 1.00)	1.00 (0.59, 1.00)
Positive likelihood ratio	5.00 (1.45, 17.27)	3.33 (1.29, 8.59)
Negative likelihood ratio	0.00 (0.00, NaN)	0.00 (0.00, NaN)
Diagnostic accuracy	0.86	0.80
Diagnostic odds ratio	Inf	Inf
Number needed to diagnose	1.25	1.42
Correlation	0.994	0.990

Discussion

Comparison of Error Grid Analysis

The percentage value of EGA output from non-invasive biomarker devices compared to commercial Blood Glucose (BG) monitoring systems to determine whether it is feasible to be applied to humans directly and produced. This percentage of the EGA zone refers to the International Standard Organization (ISO) 15197: 2016 [25,26,31]. The clinical accuracy device value of 100% the same as the Accu-Check Active BG, Bionime Rightest GM-300, and better than other commercial products (Table 2) [31].

The commercial BG monitoring system used as a comparison made from the production of several countries is Roche Diagnostic-Indianapolis, Bayer Consumer Care AG-Switzerland, Beurer GmbH & Co. KG-Germany, Bionime Corp-Taiwan, MHC Medical Producs, LLC-Taiwan, Terumo Corp-Japan, Allmedicus Co. Republic of Korea, LifeScan Inc.-California, Abbott Diabetes Care Ltd.-England, 77 Electronics Kft.-Hungary, Home Diagnostics, Inc.-Florida and AgaMatrix-United State [31].

TABLE 2. Poin estimates of EGA

Blood Glucose Monitoring System	Clarke Error Grid Zone Factor				
	A (clinically accurate)	B (error tolerance)	C (overcorrection)	D (failure to detect)	E (errors)
Biomarker Non-Invasive Devices					
Light source 1200 nm	100.0%	0.00%	0.00%	0.00%	0.00%
Light source 1300 nm	100.0%	0.00%	0.00%	0.00%	0.00%
Biomarker Commercial Products					
Accu-Check Active BG	100.0%	0.00%	0.00%	0.00%	0.00%
Bayer Contour TS	90.00%	10.0%	0.00%	0.00%	0.00%
Beurer GL - 30	89.80%	4.60%	0.00%	5.60%	0.00%
Bionime Rightest GM-300	100.0%	0.00%	0.00%	0.00%	0.00%
Easy Touch Glucometer GCU	0.00%	33.3%	0.00%	0.00%	66.6%
FineTouch	93.80%	4.60%	1.60%	0.00%	0.00%
GlucoHexal	78.00%	14.5%	1.00%	6.50%	0.00%
OneTouch Uultra Easy	99.00%	1.00%	0.00%	0.00%	0.00%
Optium Xceed (F)	99.00%	1.00%	0.00%	0.00%	0.00%
SensoCardPlus	99.00%	0.50%	0.00%	0.50%	0.00%
Stada Glucocheck	85.50%	9.50%	0.00%	2.00%	0.00%
Wellion Linus	99.00%	1.00%	0.00%	0.00%	0.00%

Pearson Comparison of The Blood Glucose Biomimetics Measurement

Pearson correlations of each incident light source from the LED wavelength and the Fourier Transform-Near InfraredFlex-N500 Buchi are showed (Fig. 2). From the plot, we know that the wavelength with a wavelength of 1200 nm has a better reading of the glucose level compared to the wavelength range of 1300 nm.

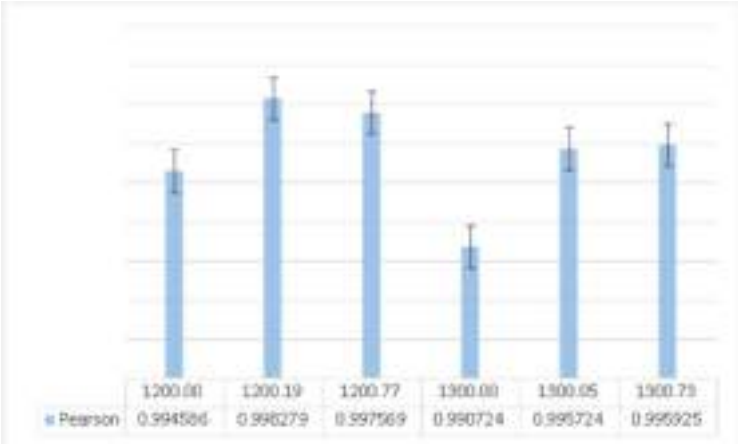

FIGURE 2. Pearson correlation reflectance values of biomarkers non-invasive devices wavelength 1200 nm, 1300 nm and Fourier Transform-Near InfraredFlex-N500 Buchi wavelength 1200.19 nm, 1200.77 nm, 1300.05 nm, and 1300.73 nm.

Non-invasive glucose measurement is a wise choice to continue to be developed and applied as a diagnostic parameter, its use without causing risk, infection, body reaction, and blood samples. When compared with Pearson values on the invasive method, non-invasive biomarkers are still better. Pearson value in testing arterial glucose concentration (Agluc) is 0.940, capillary glucose concentration (Cgluc) is 0.828, and venous glucose concentration (Vgluc) is 0.854. The level of discrepancy values respectively is 25%, 15% and 22% [32].

Pearson values in the range of categories ideally confirm that the 1200 nm LED is a suitable module for the non-invasive biomarker reflectance method. The ratio of glucose absorbance at 1200 nm wavelength is at 0.0-0.1, making it the best candidate for reflectance. From absorbance observing at the wavelength of 1500 nm-2500 nm, the wavelength of 1900 nm is an ideal candidate [33]. Investigation on the LED carried out in this study, so it needs to investigate further whether the wavelength can use as a li1ght source module for the reflectance method.

A Simulation Tool for Measuring Blood Glucose Biomimetics

In-vitro research on glucose requires a tool as a form of simulation such as a human biological. At the scale of this study, applying an approach with materials that have measurable parameters such as biological conditions. It is intended for data purity from the influence of noise factors when measuring. The purity of the measurement data is the main parameter or as a primary reference for the development of in-vivo research. The use of light sources as a means of measuring glucose is a complex process. The consideration of the emissivity factor of light is a determinant of the success of the reading of reflected light which carries glucose information on biofluids. Emissivity is a luminescence of the efficiency of a material. The value of luminescence is interpretation as the efficient ability of a material to radiate energy. Energy luminance is influencing by the factor of the surface shape, material, thickness, and transparency of a material [34].

Transparent uv-cuvette ultra-micro made from quartz has an emission level of 93% and a temperature of 21˚C. Material selection from on a comparison of the actual emission value of human skin that is 99%, superior chemical resistance than other plastic cuvettes, and a minimum sample volume [35,34]. The process of physically minimizing noise on glucose measurements using a 3D printer print probe [16].

3D printing filament used is a silk type polylactic acid (PLA). PLA the best choice because of its biodegradable and compostable [36, 37]. Furthermore PLA also has tensile elastic modulus 2890 ± 14.14 MPA, tensile strength 58.45 ± 0.55 MPa, tensile elongation 2.45 ± 0.10%, residual mass 0.36% at temperature 799.5˚C, emission visibility 0.96, solar absorption 0%, peak reflection coefficient 0.15 at a wavelength of 25 μm [37,38].

In the absorption and transmittance measurement methods, the use of black probes is ideal for minimizing noise [21,22]; however, not on the reflectance method. The ability of colours to absorb waves or temperature determines success in the process of measuring the reflectance method. Dark colours like black can absorb radiation maximally and quickly compared to bright colours like white. The characteristics of white colour have a low absorbance and can optimal to reflect light. The reflectance measurement process depends entirely on reflection either from biomimetics [39].

The filament probe material is not a consideration to minimize noise if using auxiliary material to reflect incident light. The reflector material is ideally not reacting to incident light, so it does not become information noise about what it reflects. This research utilizes a silk filament printer material to help reflect. Filament silk material can reflect light compared to other fiery materials because it is from polylactic acid and polyester composites with a ratio of 10-20%. The extruded PLA silk is 190-220°C and produces shiny, pearlescent, and higher print stability characteristics than ordinary PLA. The optimal print structure is above the thickness of 0.1 mm [40].

The recommended and standardized reflector material for measurement with a near-infrared light source is metal oxide. A metal oxide is a use in the Buchi Labortechnik AG-NIRFlex N500 analyzer as a sample reflecting device [41]. The interaction of matter with the light always begins with the process of absorption. The energy from light is radiated in the form of reflection or released to neighbouring particles. The next question is whether the information reflected by glucose on the probe carries information about the value of the glucose level or information from the probe material. Further investigation needs to will be done to confirm the reflection information [42].

CONCLUSIONS

Based on research and results, the 1200 nm LED incident light source is the best candidate to be used as a biomarker module in non-invasive reflectance methods. LED 1200 can be applied to measurements in-vitro in blood glucose biomimetic. This research was proven the pearson value of 0.99, a minimum error measurement of 8.08 mg/dL at every 1.25 repeat measurements and 100% clinical accuracy in the clarke and parkes error grid zone factor.

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We declare no competing interest.

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