



# Comparative accuracy of optical sensor-based wearable system for non-invasive measurement of blood glucose concentration

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## ARTICLE INFO

### Keywords:

Diabetes

Glucose level

Non-invasive glucometry

Optical biosensor

## ABSTRACT

Non-invasive biosensors for indirect evaluation of routinely-measured blood components by sweat analysis have broad potential clinical applications. This trial tested a wrist-borne non-invasive glucose monitor (NIGM) to measure blood glucose (BG) levels using photoplethysmographic (PPG) optical sensors. Our aim was to determine the accuracy of the device in comparison with a standard, invasive clinical method for blood glucose monitoring.

Adult participants ( $n = 200$ ) of both sexes from 18 to 75 were recruited for the study. Exclusion criteria: hemophilia and other serious coagulation disorders, impaired venous access, other serious medical conditions. A biosensor was placed on the right wrist of each participant for a non-invasive indirect BG measurement. In parallel, blood from the antecubital vein was collected and glucose levels were assessed with YSI 2300 Bioanalyzer.

The measurements were performed twice: before and after food intake, with a 1-h interval between measurements. There were no limitations to food type and quantity.

In both antepandrial ( $\rho = 0.8994$ ,  $p < 0.0001$ ) and postprandial ( $\rho = 0.9382$ ,  $p < 0.0001$ ) glucose measurements, NIGM correlated with values obtained by the YSI 2300 reference device – there was no significant difference between the two methods. Plotted on a Parkes Error Grid for Type II diabetes, NIGM readings did not deviate from those of the YSI 2300 in any clinically-significant way, with the majority of correlated readings falling within Parkes zone A. Very few readings fell within Parkes zone B. In antepandrial measurements, the mean bias between methods for all patient volunteers was  $3.705 \pm 7.838$ . In postprandial measurements gave a mean bias of  $1.362 \pm 10.15$  for all patient glucose data.

The mean absolute relative difference of currently available glucometer models ranges from 5.6% to 20.8%. The NIGM falls in the lower end of this error range at 7.40–7.54%, indicating that PPG-chemochrome sensors are capable of producing results comparable with those of direct measure glucometers. Data presented here demonstrates the reliability and accuracy of the NIGM system as an adjunctive, and perhaps substitutive, non-invasive tool for blood glucose monitoring.

## 1. Introduction

Patients with diabetes mellitus must routinely monitor their blood glucose (BG) to better manage their condition [1], as BG levels outside the reference range affect patient health and may lead to severe complications including weight change, neurologic symptoms, seizures, coma and even death [2]. Currently available methods for BG testing are invasive, cause discomfort for patients and are costly for the health care system [3]. Reliable and comfortable methods for real-time, non-

invasive measurement of BG would significantly improve treatment efficacy and would also facilitate early detection of metabolic syndrome. Further, the potential for continuous real-time monitoring of BG would allow clinicians to add another dimension to patient health assessment not widely available at present, providing a profile of daily BG fluctuations.

Biosensors for patient monitoring by sweat analysis are a promising solution for non-invasive testing as components of this easily-accessible body fluid can provide useful information on a number of blood

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<https://doi.org/10.1016/j.clinbiochem.2018.12.014>

Received 13 September 2018; Received in revised form 17 December 2018; Accepted 31 December 2018

Available online 07 January 2019

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analytes such as microelements, chemicals, hormones, drugs and their metabolites [4]. Several biosensor-based technologies are currently being developed for detection of blood glucose levels through measurement of analytes secreted in sweat, as it has been established that a strong correlation exists between levels of glucose metabolites in sweat and glucose levels in blood [5,6]. Most of the emerging sensor technologies employ amperometric biosensors, which have been documented to be a relatively accurate tool under certain environmental conditions, yet their effectiveness and accuracy can be affected by changes in skin temperature and pH. Furthermore, technologies based on this method require sweat collection, stable sensor-skin contact, and have a disposable element that needs to be replaced after single use [7,8].

Photoplethysmogram (PPG) sensing technology is an approach for non-invasive measurement under differing environmental conditions. Basically, PPG sensors work by illuminating the skin and quantifying changes in light absorption caused by expanding and contracting of blood vessels. This technology is currently used for detection of heart rate, blood pressure, blood oxygen saturation etc. [9–11]. Recent studies showed that PPG sensors can be used to predict hypoglycemic episodes by analyzing heart rate variability [12,13]. They can also be employed to evaluate BG levels based on near infrared spectroscopy, but the accuracy of this method is relatively low [14–16]. In this study, we used a non-invasive glucose monitor (NIGM) technology developed by Spectrophon, Ltd. (Israel) that employs PPG sensors coupled with an optically-sensitive coating that changes its optochemical parameters in presence of specific compounds in sweat, which are then analyzed by a proprietary algorithm to derive blood glucose concentrations [17].

The main objective of the study was to evaluate the reliability and accuracy of NIGM for BG measurement. The accuracy was estimated by comparison of NIGM against a commercially-available glucometer, the YSI 2300 STAT Plus Glucose and L-Lactate Laboratory Bioanalyzer (YSI 2300), which is a recognized standard for the measurement of BG levels.

## 2. Materials and methods

### 2.1. Biosensor detection device

The biosensor incorporated into Samsung Gear S2™ smartwatch consists of PPG optical element and backglass panel containing a compound, which changes optical characteristics in presence of certain metabolites (water, lactate, pyruvate, carbonate, ketones, sodium, potassium) in sweat (US patents pending US20150260656A1, US20170027482A1). Different concentrations of listed metabolites affect the behavior of the chemochromic detection system, changing the signal output, which is transmitted by Bluetooth to the application on a smartphone. The transferred data is then transformed to blood sugar concentration (mg glucose/dL blood) using a proprietary algorithm (Spectrophon firmware version 1.7).

### 2.2. Study population

A nonrandomized, nonblinded glucose-detecting NIGM study with human volunteers was carried out in accordance with the guidelines of Helsinki Committee and was approved by the ethics committee in Maale Carmel Mental Health Center, Israel (N 06/17). An informed consent form was signed by all patients prior to study participation.

Adult participants (n = 200) of both sexes from 18 to 75 able to give informed consent were recruited for the study. Exclusion criteria were as following: hemophilia and other serious coagulation disorders, significantly impaired venous access, or any other serious medical conditions. Participants had the option to withdraw from the experiment at any point.

### 2.3. Reference device

A YSI 2300 STAT PLUS Glucose and L-Lactate Bionalyzer (Yellow Springs Instruments) was selected as a blood glucose reference method since it is accepted as a valid laboratory reference method for blood glucose measurement by the US Food and Drug Administration (FDA). Daily instrument calibration was performed to ensure device accuracy and data quality using glucose standard solutions (Glucose Standard 10 mmol/L, Yellow Springs Instruments) adhering to National Institute of Standards and Technology (NIST) guidelines.

### 2.4. Experimental design and blood glucose detection

A Samsung Gear S2 smartwatch with integrated biosensor was placed on the right wrist of each participant for a non-invasive indirect measurement of BG level. In parallel to glucose measurements with NIGM, blood from the antecubital vein was collected by a certified healthcare professional. Glucose levels in collected blood were assessed with YSI 2300.

The measurements were performed twice: before and after food intake, with a 1-h interval between measurements. There were no limitations to food type and quantity. All experiments were performed indoors under ambient temperature (22–24 °C) and humidity (40–60%).

Results obtained from NIGM were automatically archived on a mobile phone connected via Bluetooth to a Samsung Gear S2. Manual recording of data was also performed.

Skin of subjects was examined after the procedure for allergic reactions or contact dermatitis caused by use of the NIGM.

### 2.5. Data statistical analysis

Mean absolute percentage error (MAPE) was calculated between the values obtained by NIGM versus the YSI 2300 and compared by unpaired Student's *t*-test to evaluate whether there is a significant difference in data output between devices.

The NIGM accuracy was measured by means of a correlation analysis. Linear regression was used to produce the graphical plot of the NIGM values vs. YSI 2300 values. The correlation coefficient (Pearson's Rho:  $\rho$ ) was calculated using the Pearson regression method. Mean bias, MAPE (mean absolute percent error), %NRMSE (percent normalized root mean square error), and MAE (mean absolute error) were calculated on the total patient data set using the formulae presented in Fig. S1.

Compliance with accuracy requirements stipulated in ISO 15197:2013 for over-the-counter use (consumer) glucometer devices was evaluated, defined as follows:

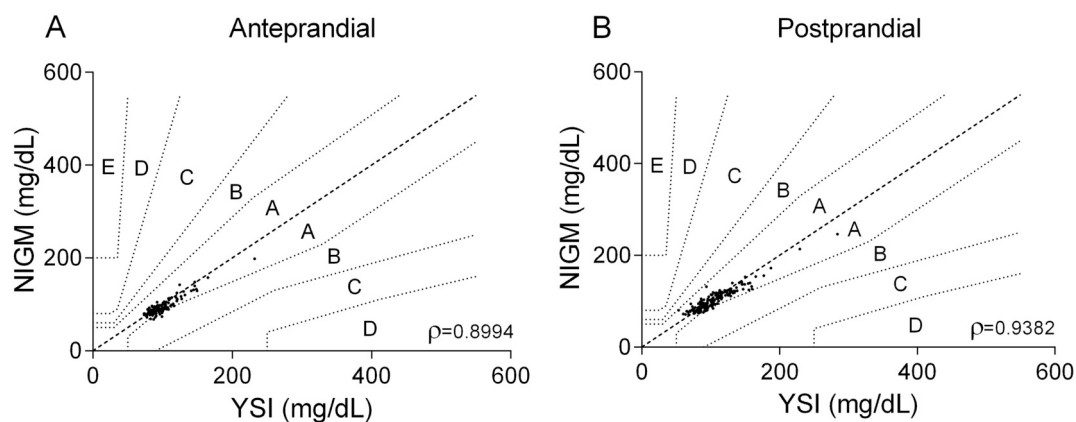
Standard 1 (ISO15): 95% of all measured BG meter values must be within 15% of the true value for glucose levels if  $\geq 100$  mg/dL and within 15 mg/dL of the true value for glucose levels  $< 100$  mg/dL. Standard 2: At least 99% of measurement results shall fall within the Consensus Error Grid (Parkes) zones A and B.

Accuracy standards were additionally assessed by criteria stipulated in FDA-2013-D-1446 (2016) for over-the-counter (consumer) glucometer devices as follows:

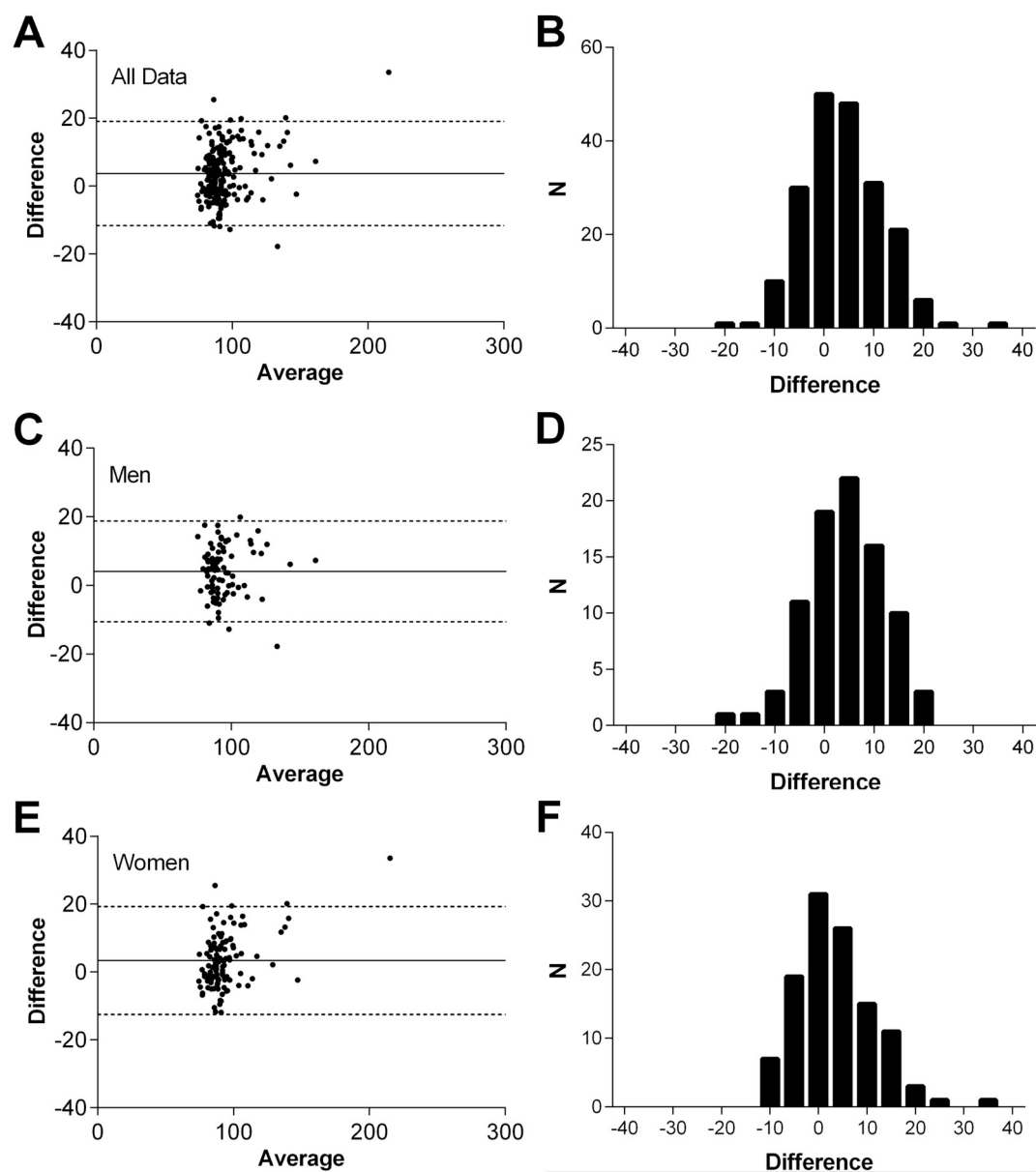
Standard 1 (FDA15): 95% of all BG results in this study are within  $\pm 15\%$  of the comparator results across the entire claimed measuring range of the device.

Standard 2 (FDA20): 99% of all BG results are within  $\pm 20\%$  of the comparator results across the entire claimed measuring range of the device.

This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as #NCT03359629.



**Fig. 1.** Correlation of BG measures between YSI 2300 and NIGM on a Parkes Error Grid in (A) anteprenalial ( $\rho = 0.8994$ ,  $p < 0.0001$ ) and (B) postprandial ( $\rho = 0.9382$ ,  $p < 0.0001$ ) readings.



**Fig. 2.** Bland-Altman plot comparison of anteprenalial YSI 2300 and NIGM glucometer readings for (A) all patients, (C) men, and (E) women. Frequency distributions of glucometer reading differences between YSI 2300 and NIGM for (B) all patients, (D) men, and (F) women.

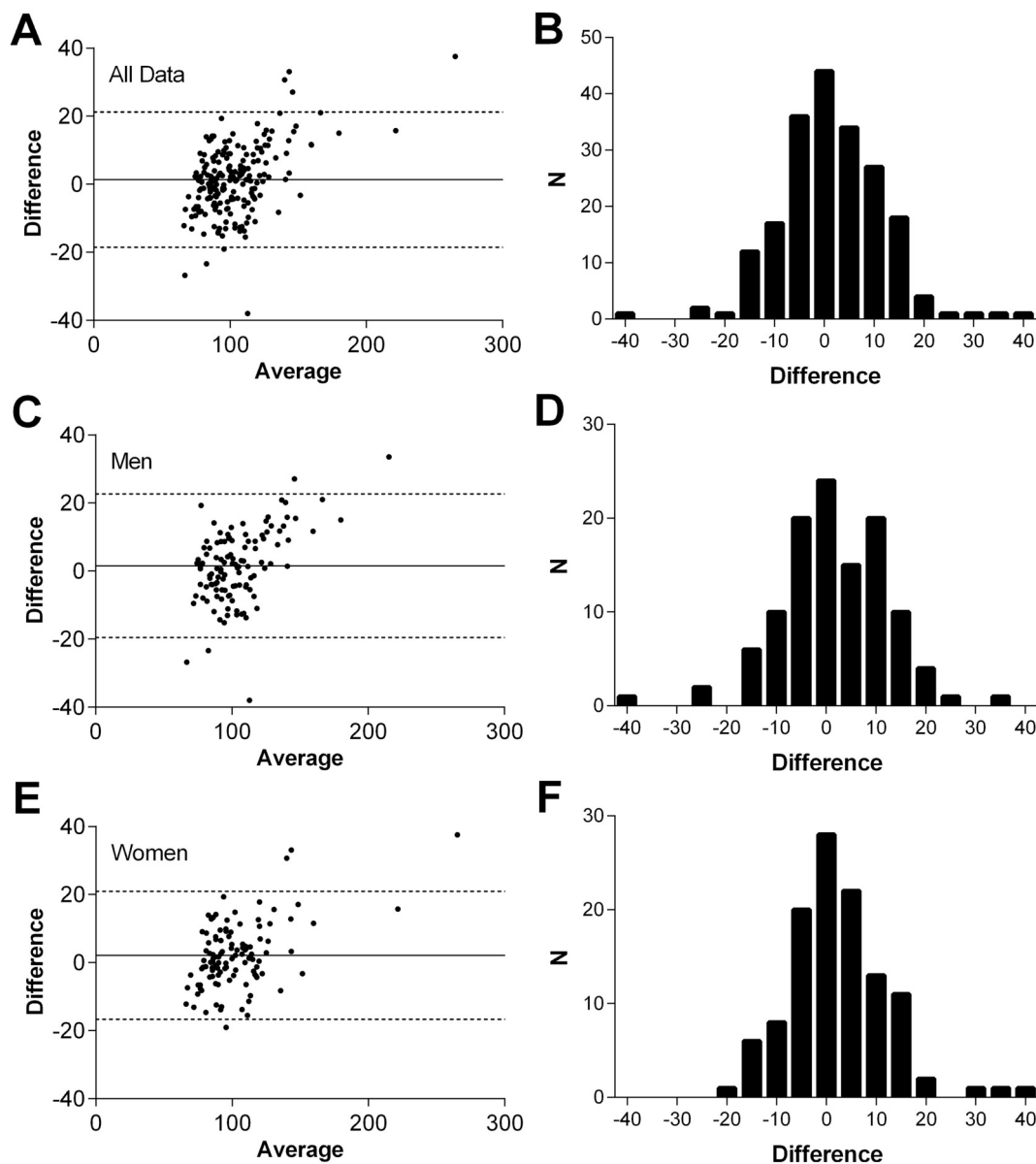


Fig. 3. Bland-Altman plot comparison of postprandial YSI 2300 and NIGM glucometer readings for (A) all patients, (C) men, and (E) women. Frequency distributions of glucometer reading differences between YSI 2300 and NIGM for (B) all patients, (D) men, and (F) women.

### 3. Results

NIGM precision data were provided by the manufacturer (Spectrophon) and had consisted of triplicate reads through an artificial skin membrane of artificial sweat (Fig. S2). Device precision was linear across the examined blood glucose range (50–350 mg/dL;  $r^2 = 0.9818$ ).

All study participants completed the planned procedures with no adverse events.

In both anteprenal (p = 0.8994, p < 0.0001) and postprandial (p = 0.9382, p < 0.0001) glucose measurements, NIGM correlated with values obtained by the YSI 2300 reference device (Fig. 1A, B). Plotted on a Parkes Error Grid for Type II diabetes [18,19], NIGM readings did not deviate from those of the YSI 2300 in any clinically-significant way, with the majority of correlated readings falling within Parkes zone A. Very few readings fell within Parkes zone B (affects clinical decision-making with negligible effects on clinical outcome): (Fig. 1A) anteprenal measures, 5/200 readings (2.5%); (Fig. 1B) postprandial measures, 3/200 readings (1.5%). There were no significant sex- or age-dependent differences between the YSI 2300 and NIGM output

(p > 0.50; data not shown).

Examination of measurement agreement between the YSI 2300 reference device and the NIGM indicated no significant difference between the two methods. In anteprenal measurements, the mean bias between methods for all patient volunteers was  $3.705 \pm 7.838$  (mean  $\pm$  SD, including all subsequent bias measures; Fig. 2A). Subdividing the readings by sex, no significant trends in mean bias were noted for readings obtained with men ( $4.117 \pm 7.491$ ; Fig. 2C) or women ( $3.394 \pm 8.109$ , Fig. 2E). In all anteprenal measures, distribution of differences in measures between methods varied normally around the mean value with high kurtosis (all data, Fig. 2B: 0.4728; men, Fig. 2D: 0.3716; women, Fig. 2F: 0.9685), indicating tight clustering around the mean.

Similar examination of measurement agreement between YSI 2300 and NIGM in postprandial measures gave a mean bias of  $1.362 \pm 10.15$  for all patient glucose data (Fig. 3A). No significant trends in mean bias were observed when data was subdivided by sex into male ( $1.573 \pm 10.76$ ; Fig. 3C) and female data sets ( $2.163 \pm 9.594$ ; Fig. 3E). Distribution of differences between methods

**Table 1**  
Summary statistical comparisons between YSI 2300 and NIGM BG readings.

		Anteprenalial	Postprandial
Mean Bias	mg/dL	3.71	1.36
	%	3.86	1.31
MAPE	Mean	7.40	7.54
	%95CI	6.6–8.2	6.6–8.5
	%SD	± 5.90	± 6.58
%NRMSE		11.56	9.79
MAE	mg/dL	6.77	7.77
	SD	5.40	6.65
ISO15	%	95.5	97.0 <sup>a</sup>
	N	191	193 <sup>a</sup>
FDA15	%	95.0	95.0 <sup>a</sup>
	N	190	189 <sup>a</sup>
FDA20	%	99.5	99.0 <sup>a</sup>
	N	199	197 <sup>a</sup>

Abbreviations: MAPE, mean absolute percent error; %95CI, 95% confidence interval limits of MAPE; %SD, percent standard deviation of MAPE; %NRMSE, percent normalized root mean square error (using an unbiased estimator correction); MAE, mean of mean absolute errors; SD, standard deviation of MAE. ISO15, number of mean patient NIGM readings (N) and percent total (%) which fell within the boundaries of the ISO 15197:2013 Standard 1. FDA15, number of mean patient NIGM readings (N) and percent total (%) which fell within the boundaries of FDA OTC Standard 1; FDA20, number of mean patient NIGM readings (N) and percent total (%) which fell within the boundaries of FDA OTC Standard 2. N = 200 subjects.

<sup>a</sup> One subject in postprandial readings elected not to undertake a second set of blood draws.

in postprandial measures varied normally around the mean value with a flatter kurtosis for all patient data and men alone (all data, Fig. 3B: −0.2162; men, Fig. 3D: −0.3407), whereas measurement differences between methods tended to remain tightly clustered around the mean value for women (women, Fig. 3F: 0.5861).

Mean bias percentages between YSI 2300 and NIGM were low (3.86% anteprenalial, 1.31% postprandial). Similarly, mean absolute percent error values (MAPE) were also low, with narrow 95% confidence intervals (mean %, 95% confidence interval in percent; anteprenalial: 7.4%, 6.6–8.2%; postprandial: 7.54%, 6.6–8.5%). Differences between anteprenalial and postprandial MAPE were not significant (Student's *t*-test, *p* = 0.8229). Normalized root mean square error was 11.56% anteprenalial and 9.79% postprandial, both of which were less than the expected 15%. In a similar manner, mean absolute error (MAE) values between the two methods were low for both anteprenalial (6.77 ± 5.40, mean ± SD) and postprandial (7.77 ± 6.65, mean ± SD) measures. Differences in MAE for anteprenalial and postprandial measures were not significant (Student's *t*-test, *p* = 0.1022). Furthermore, the NIGM passed both criteria of the ISO 15197:2013 and FDA-2013-D-1446 standards. A summary of the aforementioned statistical measures is presented in Table 1.

#### 4. Discussion

The use of an accurate, reproducible, non-invasive method for measuring changes in blood chemistry, for example glucose level, outside of a medical laboratory environment through devices available to consumers with minimal technical knowledge has always been an attractive prospect. Various attempts at developing a reliable non-invasive glucometer have been made, with focus on optical [5,16,20–22] and electrochemical [8,15,23] methods. Many of these biosensing methods are, however, prone to error, sensitive to varying environmental conditions, and to date no reliable non-invasive glucose measurement device has been developed to fill this clinical need [7,8,24] PPG sensors have proven their reliability in measuring heart rate, oxygen saturation, blood pressure, and cardiac output applications [9–11]. The major purpose of this work was to evaluate suitability and

accuracy of non-invasive PPG-based biosensor technology coupled with a chemochromic coating for measurement of physicochemical blood parameters in comparison with approved, invasive clinical methods for blood glucose monitoring. Here we demonstrate a reliable means of non-invasive glucose testing by use of the NIGM as a wearable device, which requires no direct contact with blood or blood products.

The technology tested in the current study, NIGM, utilizes specific components of sweat to produce reliable and reproducible results indistinguishable from direct, chemical measures of BG. Performance of the NIGM was comparable to that of commercially available direct-measurement glucometers. In an accuracy study of 17 glucometer models [25], the mean absolute relative difference (MARD or MAPE) of glucometer models in overall measures ranged from 5.6% to 20.8%. The NIGM presently utilized falls in the lower end of this error range at 7.40–7.54%, indicating that PPG-chemochrome sensors are capable of producing results comparable with those of direct measure glucometers. We also did not observe any changes in NIGM accuracy at low (60–80 mg/dL) or high (> 200 mg/dL) levels of BG (data not shown), thus demonstrating its applicability across the full range of human BG values. It should be noted, however, that this study was executed under constant environmental conditions, which may have allowed for the reduction in error.

The current findings represent a continuation of a recently published preliminary study, which proposed the use of NIGM device for BG analysis [17]. Two limitations of the former accuracy study, namely its relatively small sample size (*n* = 30) and comparison with the home-use *Accu-Chek Aviva* glucose monitor, are overcome in the present study. The greater statistical power afforded presently by 460 independent glucose measurements, each measurement conducted in tandem with a clinical diagnostic device, markedly enhance the confidence with which we may suggest the reliability of the novel device. Rigorous MAPE analysis confirmed the accuracy of the present findings, further supporting the advancement towards clinical application of NIGM technology for diabetes care.

#### 5. Conclusion

The ease of use and anticipated relative low-cost of producing and distributing devices such as the NIGM should facilitate patient compliance in blood sugar monitoring and provide an easily accessible tool to improve patient health. Further, the developed biosensor technology enables patients to collect and report a blood sugar level history, rather than a single measure “snapshot” of BG. We anticipate that BG dynamics over time should empower physicians with an additional level of information to assist in improved clinical decision-making and thereby improve patient wellness outcomes.

#### Author contributions

Dr. D. Rodin wrote the manuscript and obtained data. Dr. M. Kirby carried out statistical analysis and edited the manuscript, Dr. N. Sedogin collected blood samples and NIGM data, Prof. Y. Shapiro, Prof. A. Pinhasov, Prof. A. Kreinin reviewed and edited the manuscript, Prof. A. Pinhasov, Prof. A. Kreinin and Dr. Rodin designed, organized and controlled the research process, Prof. A. Pinhasov is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

#### Funding

This work was supported by the Institute for Translational Research (Ariel University, Israel) and Spectrophon LTD, Israel (RA1700000364). Dr. Rodin's Post-doctoral fellowship was partially funded by the Ministry of Aliyah and Integration, Israel.

The views expressed are those of the authors and not necessarily

those of the Institute for Translational Research or Spectrophon LTD.

## Conflict of interest

The authors declare no competing financial or non-financial interests.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinbiochem.2018.12.014>.

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