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Logistic regression analysis for identifying the factors affecting development of non-invasive blood glucose calibration model by near-infrared spectroscopy

Yasuhiro Uwadaira [a], Ayaka Shimotori [b], Akifumi Ikehata [a,*], Keiko Fujie [c], Yoshio Nakata [c], Hiroaki Suzuki [d], Hitoshi Shimano [d], Koichi Hashimoto [c]

[a] National Food Research Institute, NARO, 2-1-12 Kannondai, Tsukuba, Ibaraki 305-8642, Japan
[b] Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
[c] Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
[d] Metabolism and Endocrinology, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

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ABSTRACT

This study was conducted to develop a statistical method for investigating the factors that hamper the development of individual non-invasive blood glucose calibration model using near-infrared (NIR) spectroscopy. First, the individual calibration models for the patients with diabetes mellitus were developed by applying partial least squares regression to relate data of NIR spectra measured at the hand with blood glucose concentrations. Second, items obtained via medical examinations were analyzed using logistic regression in order to specify the factors that hamper the development of successful models. Consequently, the individual calibration models for approximately 40% of patients were successfully developed with a mean standard error of cross-validation (SECV) of 25.0 mg/dL. For more than 60% of these patients, over 80% of the validation samples fell within zone A of the Clarke error grid representing clinically acceptable accuracy. According to the results of logistic regression analyses, body mass index (BMI) which may affect the variation in physical measurement conditions was considered to be an effective factor for developing successful calibration models besides the change in blood constituents. A statistical approach using logistic regression analysis represents a novel efficient method for investigating the factors contributing to develop successful individual calibration models.

1. Introduction

Approximately 382 million people worldwide, or 8.3% of adults, were estimated to have diabetes in 2013, and with expected increases in incidence, more than 590 million individuals worldwide are expected to have type 2 diabetes by 2035 [1]. People with diabetes have an increased risk of developing a number of serious health problems. Therefore, in order to prevent and treat such complications, diabetic patients require appropriate control of blood glucose levels by self-monitoring of these values several times a day. The established self-monitoring of blood glucose (SMBG) methods require a drop of a blood sample from a finger; therefore, the associated pain, trouble, and cost of the test strips represent a great burden for diabetic patients.

Thus, *in vivo* non-invasive blood glucose measurement techniques are attractive tools for diabetic patients. Lots of studies have been performed to achieve this goal, using a variety of technologies such as optical spectroscopy, electromagnetic sensing, fluorescence technology, or impedance spectroscopy [2,3]. Although several companies to date have introduced various products, they lack the precision and specificity of a blood glucose meter [4]. The near-infrared (NIR) spectroscopy has received the most attention, however many attempts to develop NIR-based techniques lacked robustness for *in vivo* use [5]. The fundamental problem is that the glucose specific signals are too small to accurately distinguish from the background absorption of the tissue components such as water, fat or protein. Individual differences due to the complexity of human biological tissues are also one of the most serious problems for developing a universal technique that can be applied to the general population.

Our previous studies demonstrated the potential of using NIR spectroscopy for non-invasive blood glucose measurements [6,7]. Although it has thus far not been possible to develop a universal calibration model for the general population using our technique, the individual calibration models can be successfully built for a portion of subjects. The investigation of the factors determining the success or failure for

* Corresponding author. Tel.: +81 29 838 8088; fax: +81 29 838 7996.
E-mail addresses: uwadaira@affrc.go.jp (Y. Uwadaira), nenuphar1217@gmail.com (A. Shimotori), ikehata@affrc.go.jp (A. Ikehata), k-fujie@md.tsukuba.ac.jp (K. Fujie), nakata@md.tsukuba.ac.jp (Y. Nakata), hirosuzu@md.tsukuba.ac.jp (H. Suzuki), hshimano@md.tsukuba.ac.jp (H. Shimano), koichi.hashimoto@md.tsukuba.ac.jp (K. Hashimoto).

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developing individual calibration models is very important so that non-invasive techniques can be progressed to the next stage of application, nevertheless no study has thus far statistically examined such factors mainly because of the extreme difficulty in collecting a variety of data from living human subjects. In this study, we propose a statistical method for investigating such disturbance factors by examining the inspection items obtained from medical tests of patients with diabetes mellitus.

2. Materials and methods

A total of 32 patients with diabetes mellitus (15 males and 17 females; 10 with type 1 diabetes and 22 with type 2 diabetes) who were admitted to the University of Tsukuba Hospital participated in this study. The age of the patients was within the range of 30–75 years, with a mean of 52.7 years. The study protocol was approved by the ethics committee of the hospital. Written informed consent was obtained from all patients. First, individual calibration models were developed based on NIR spectroscopy data. Second, the inspection items of the patients' physical information and blood constituents were analyzed using logistic regression to identify the factors that determined the success or failure of developing the individual calibration model. The overall procedure of this study is shown in Fig. 1.

2.1. Developing individual calibration models for non-invasive blood glucose measurements

The patients with diabetes mellitus needed to measure their blood glucose concentration from finger-prick samples six times a day using an SMBG meter. Each patient had his or her own SMBG meter, which was either a OneTouch Ultra (Johnson & Johnson K.K.; Tokyo, Japan) meter or a Medisafe Mini (TERUMO Corp.; Tokyo, Japan) meter. The NIR spectra were measured four times a day just before the SMBG measurements were obtained. Data were collected at 10:00 a.m. and 2:00 p.m. in the postprandial state and at 11:30 a.m. and 5:30 p.m. in the preprandial state. In addition to the NIR spectra, body temperature (digital armpit thermometer, TERUMO Corp.; Tokyo, Japan), blood pressure (BP-203RV2; OMRON CLIN Co., Ltd.; Tokyo, Japan), and arterial oxygen saturation (PULSOX-1; Konica Minolta, Inc.; Tokyo, Japan) of the patients were also measured at each time point. At least 10 data sets per patient were collected during the period of hospitalization. Data collection was implemented from April to October of 2013.

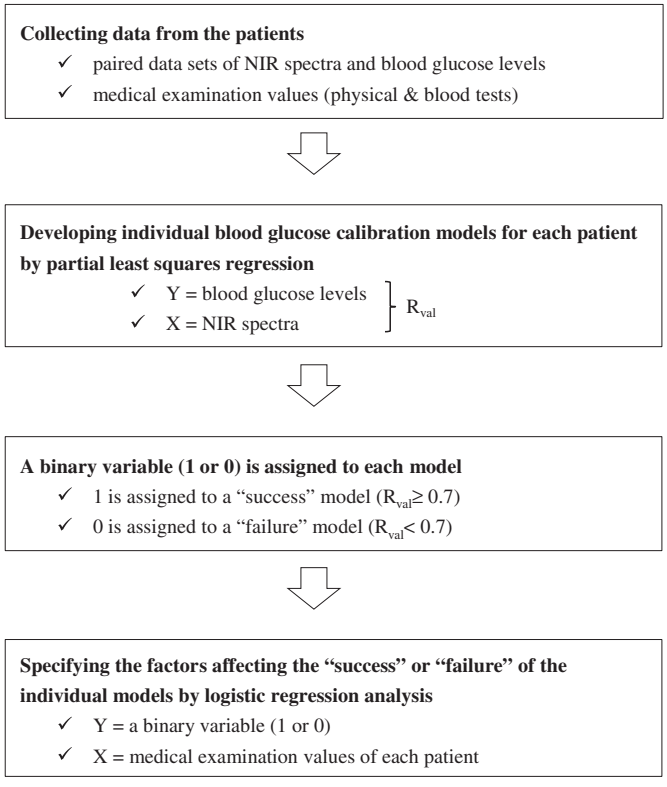

Fig. 1. Study procedure. R_{val}: correlation coefficient between the reference values and the predicted values of cross-validation.

The experimental apparatus used for non-invasive measurement consisted of a light source, a commercially available S-2930 NIR spectrophotometer (Soma Optics, Ltd.; Tokyo, Japan), a control unit (a touch-panel PC with Windows OS), and a temperature controller (Fig. 2(a)). The interactance probe was equipped with five small tungsten halogen lamps (1 W) placed in a circle within a radius of 8.5 mm, and the light guide for the spectrometer was placed at the center of the circle as shown in Fig. 2(b). The interactance probe can detect the light that is diffusely reflected in the sample. In order to control the temperature of the measurement site, a rubber heater was attached on the backside of the probe. The temperature controller adjusts the voltage supply according to the signal received from the thermocouple.

Each patient placed one hand on the probe for measuring NIR spectra, as illustrated in Fig. 2(a). The NIR diffuse reflectance spectra were collected in the wavelength region of 700–1050 nm at 1-nm intervals. Measurements were taken of a polytetrafluoroethylene plate (ϕ = 40 mm and t = 15 mm) as a reference material before the sample measurements. The palm of the hand was adopted as the measuring site, according to our previous study [6]. The temperature of the interactance probe was maintained at 36.0 ± 0.1 °C before starting the measurement. Each spectrum was taken as the average of 50 scans with an exposure time of 300 ms, and required 15 s to record.

The individual blood glucose calibration models for each patient were developed by applying partial least squares (PLS) regression [8]. Data were analyzed using a custom-designed program written in R (The R Foundation) with the "pls" package. Full cross-validation (leave-one-out) [9] was used to evaluate the calibration models. Samples with a standard error of cross-validation (SECV) ≥ 2σ (σ is the standard deviation of SECV) were removed as outliers.

2.2. Identifying the factors affecting the success of individual calibration model development

The factors examined in this study were the inspection items obtained by medical examinations performed in the hospital, including physical and blood (biochemistry and complete blood count) tests. The correlation coefficient of the cross-validation (R_{val}) obtained from the calibration model for each patient was used to judge whether or not the model was developed successfully. Specifically, a model with $R_{val} \geq 0.7$ was considered to be a "success" in this study. We did not use the SECV to judge the success of the model because the SECV may be small even if the model does not fit well because of the narrow fluctuation range of blood glucose levels. According to the criterion, a binary variable (1 or 0) was assigned to each model, corresponding to "success" ($R_{val} \geq 0.7$) or "failure" ($R_{val} < 0.7$), respectively. This binary variable was used as the objective variable, and the inspection items were used as the explanatory variables for the binomial logistic regression analysis. The logistic regression model is appropriate for the response variable based on a series of "yes"/"no" responses [10]. In this case, it estimates the probability that an individual calibration model will be built as "success" ($R_{val} \geq 0.7$) and this probability was expressed as the function of the explanatory variables. In cases for which several medical examinations were performed for a single patient, the mean values of each inspection item were adopted. The logistic regression was performed using a custom program written in R language with the "stats" and "epicalc" packages. Multicollinearity of the explanatory variables was verified by calculating the variance inflation factor (VIF) [11], and variables with a VIF ≥ 5.0 were excluded from the explanatory variables.