Development of HRV-Based Biomarkers for Predicting Blood Glucose Levels

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***Abstract*— The objective of this study was to develop electrocardiography (ECG)-based biomarkers for predicting blood glucose levels. Resting-state ECG signals were recorded from lead I for a six-minute period, and 21 heart rate variability (HRV) features were extracted. To identify potential biomarkers for non-invasive blood glucose monitoring, we performed correlation analyses between the 21 HRV features and blood glucose levels. Four HRV features demonstrated statistically significant correlations with blood glucose levels: α2, PIP, and IALS showed negative correlations, while HF power was positively correlated. These results highlight the potential of ECG-based HRV features as non-invasive biomarkers for estimating blood glucose levels in daily life.**

I. Introduction

Diabetes is a chronic metabolic disorder characterized by sustained hyperglycemia due to impaired insulin secretion. It can lead to serious complications such as cardiovascular disease and stroke [1]. According to the International Diabetes Federation, approximately 588 million individuals worldwide have diabetes, and about 487 million are estimated to have impaired fasting glucose [2]. In particular, glucose levels can be often normalized through lifestyle modifications such as dietary control and physical activity in the prediabetic stage. Therefore, regular glucose monitoring is important not only for individuals with diabetes but also for those at risk [3].

However, conventional blood glucose monitoring methods are primarily invasive, often causing discomfort for both diabetic and non-diabetic individuals. As a result, many people are reluctant to undergo regular glucose testing. Therefore, it is essential to develop non-invasive blood glucose monitoring methods that are convenient for daily use, even among non-diabetic populations.

Heart rate variability (HRV), derived from heart rate signals obtained through electrocardiography (ECG), has emerged as a potential non-invasive biomarker measurable via wearable devices such as smartwatches and earbuds [4]. Clinically, HRV reflects the dynamics of the autonomic nervous system and has been widely used to assess cardiovascular risks associated with diabetes [5]. Recent studies have demonstrated that ECG-based models can accurately detect hyperglycemic and hypoglycemic states in diabetic patients [6-7]. However, most of these studies have focused on binary classification–distinguishing hyperglycemic or hypoglycemic states–primarily within diabetic patients. Furthermore, few studies have incorporated nonlinear HRV features, which are known to capture signal complexity and autonomic dysfunction [8-9].

To address these gaps, the present study aims to identify HRV-based biomarkers for estimating blood glucose levels using resting-state ECG. The analysis extends beyond individuals with diabetes to include the non-diabetic population as well. A total of 21 HRV features, including nonlinear-domain metrics, were extracted for non-invasive blood glucose monitoring. Ultimately, this study evaluates the potential of HRV-based monitoring as a practical and scalable solution for non-invasive, wearable blood glucose detection.

II. Methods

A. Data acquisition

Thirty healthy participants (15 males and 15 females; mean age 21.3 ± 1.9 years) were recruited for this study. All participants were in their twenties and had no history of cardiovascular, physical, or mental disease. To measure fasting glucose levels, all participants refrained from consuming food and fluids for at least nine hours before the experiment. Blood glucose levels were obtained by averaging the readings from three commercial glucometers: ACCU-CHEK Guide and ACCU-CHEK Instant (Roche, Switzerland), and CareSens N Premier (i-SENS, Korea) (Fig. 1(a)). Resting-state ECG was recorded using a lead-I configuration (Fig. 1(b)).

Fig. 1(a) Blood glucose measurement devices (b) Lead I ECG

Table 1. HRV feature

HRV feature	full term	HRV feature	full term
RRI	RR interval	nuVLF	normalized VLF
SDNN	standard deviation of normal-to-normal (NN) intervals	SD1	standard deviation 1
RMSSD	root mean square of successive differences	SD2	standard deviation 2
pNN50	percentage of NN50	α1	short-term fluctuation exponent
HF	high-frequency power	α2	long-term fluctuation exponent
nuHF	normalized HF	SampEn	sample entropy
LF	low-frequency power	PIP	percentage of inflection points
nuLF	nomalized LF	IALS	inverse average length of segments
LF/HF	ratio of low-frequency to high-frequency	PSS	percentage of NN intervals in short segments
TP	total power	PAS	percentage of NN intervals in alternation segments
VLF	very low-frequency power		

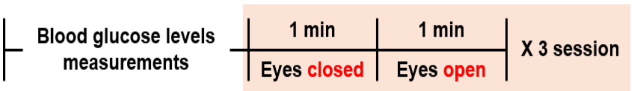

Fig. 2 Overall experimental procedure

The experiment was conducted between 9:00 a.m. and 12:00 p.m. and consisted of alternating 1-minute eye-closed (EC) and eye-open (EO) conditions, repeated three times each. Fig. 2 shows the overall experimental procedure. This study was approved by the Institutional Review Board (IRB) of Korea University [KUIRB-2023-0383-02, KUIRB-2024-0107-04].

B. Data analysis

The recorded ECG was downsampled to 200 Hz for preprocessing. A 60 Hz notch filter was applied to remove powerline interference, followed by a 5–40 Hz bandpass filter to isolate relevant cardiac frequencies. R peaks were detected, and the RR interval (RRI) was calculated. RRI values exceeding three standard deviations were considered outliers and were excluded from the analysis through visual inspection. Subsequently, 21 HRV features were extracted using PhysioZoo, a MATLAB-based toolbox designed for HRV analysis [10]. Specifically, eight time-domain features, eight frequency-domain features, and five non-linear HRV features were extracted, as summarized in Table 1 along with their abbreviations. Pearson correlation analysis was conducted to evaluate the statistical significance of the relationships between blood glucose levels and HRV features.

III. Results

Table 2 presents the results of the correlation analysis between HRV and blood glucose levels. Among the 21 HRV features, four demonstrated statistically significant correlations (Pearson correlation coefficient, $p < 0.05$). Specifically, the HF component exhibited a positive correlation, while the other three features—α2, IALS, and PIP—showed negative correlations. Notably, α2 exhibited the strongest association, with the highest correlation coefficient of $r = –0.40$ ($p < 0.05$).

Table 2. Peason correlation coefficients (r) between HRV and blood glucose levels (* $p < 0.05$)

HRV feature	correlation coefficients	HRV feature	correlation coefficients
RRI	-0.35	**nuVLF**	-0.30
SDNN	0.19	**SD1**	0.20
RMSSD	0.20	**SD2**	0.18
pNN50	0.25	**α1**	-0.16
HF	**0.37***	**α2**	**-0.40***
nuHF	0.25	**SampEn**	0.02
LF	0.22	**PIP**	**-0.38***
nuLF	0.11	**IALS**	**-0.38***
LF/HF	-0.04	**PSS**	-0.34
TP	0.32	**PAS**	-0.18
VLF	0.17		

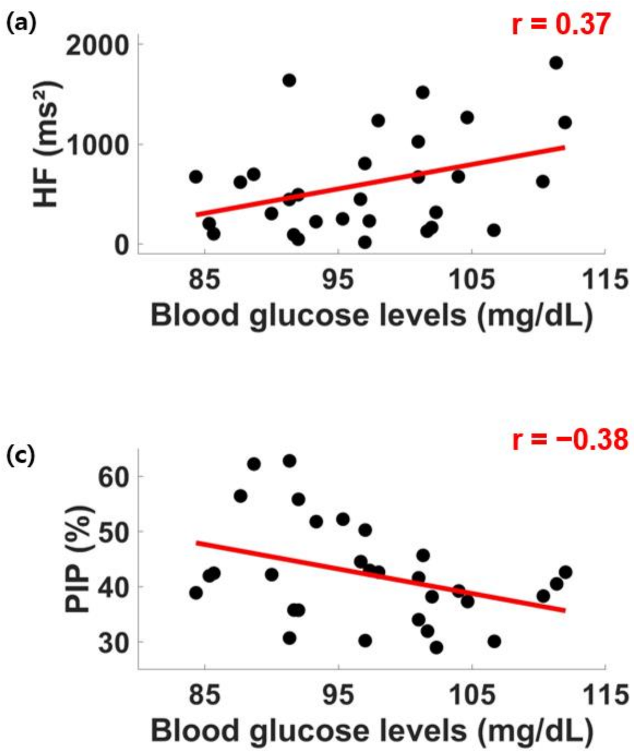

Fig. 3 Correlation between HRV features and blood glucose levels: (a) HF (b) α2 (c) PIP (d) IALS.

As shown in Fig. 3(a), HF, a frequency domain HRV metric associated with parasympathetic activity, was positively correlated with blood glucose levels ($r = 0.37$, $p < 0.05$). Fig. 3(b) presents a significant negative correlation between the α2 and glucose ($r = -0.40$, $p < 0.05$). As a nonlinear HRV metric, α2 reflects long-term fractal scaling properties. In Fig. 3(c), the Poincaré plot index PIP, which quantifies the ratio of short-term to long-term variability, also showed a negative correlation with glucose levels ($r = -0.38$, $p < 0.05$). Similarly, Fig. 3(d) illustrates a negative correlation between IALS and blood glucose levels ($r = -0.38$, $p < 0.05$).

IV. Discussion

This study aimed to identify optimal HRV-based biomarkers for predicting blood glucose levels by analyzing the correlations between HRV and fasting blood glucose levels. The results showed significant correlations between four HRV features—HF, α2, PIP, and IALS—and blood glucose levels.

Notably, three of the four features were nonlinear HRV indices, all of which exhibited significant negative correlations. The α2 showed a strong negative association with blood glucose levels. These findings suggest that impaired autonomic regulation related to glucose metabolism may manifest as reductions in both nonlinear and long-term variability. Supporting this, previous studies have shown increased sympathetic activity and diminished HRV in hyperglycemic states [6].

In addition, both the PIP and IALS showed negative associations with glucose levels. A lower PIP indicates reduced short-term parasympathetic modulation, which is consistent with previous evidence suggesting that hyperglycemia may suppress vagal tone. Similarly, decreased IALS values suggest diminished capacity for information processing in autonomic control, indicating that rising glucose levels may compromise the complexity of autonomic regulation, even in non-diabetic individuals [11].

In contrast to these nonlinear markers, HF showed a significant positive correlation with glucose levels. This finding is somewhat unexpected, as elevated glucose levels are typically associated with sympathetic dominance and reduced vagal tone. However, it may reflect individual variability among healthy individuals or compensatory parasympathetic responses under resting-state conditions [12]. This highlights the importance of considering both linear and nonlinear HRV features in early detection frameworks, while also calling for further research to determine whether this pattern indicates early adaptation or transient regulation rather than a pathological change.

To validate and expand upon these findings, it is essential to recruit a larger number of participants and examine correlations under various experimental conditions.

In summary, these findings suggest the potential of HRV features may serve as non-invasive biomarkers for early glucose dysregulation. While this study focused on correlation-based analysis in healthy individuals, further research is required to validate these findings across more diverse populations and conditions. Based on results, future studies will implement deep learning models using HRV features to estimate blood glucose levels. Ultimately, our goal is to develop a practical wearable blood glucose monitoring system for daily use in both diabetic and non-diabetic individuals.

V. Conclusions

This study aimed to identify optimal HRV-based biomarkers for predicting blood glucose levels by analyzing the correlations between HRV and fasting blood glucose levels. The analysis revealed significant correlations between blood glucose levels and four HRV features: HF, α2, PIP, and IALS. These findings suggest that HRV may serve as a meaningful non-invasive indicator for estimating glucose regulation, even in non-diabetic individuals. Notably, three of the four significant features—α2, PIP, and IALS—belong to the nonlinear domain, highlighting the relevance of nonlinear HRV dynamics in capturing subtle physiological changes related to glycemic status. Taken together, this study contributes to the growing evidence that nonlinear HRV features extracted from resting-state ECG can provide valuable insights into autonomic dysfunction and support the development of wearable tools for non-invasive glucose monitoring.

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