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Original article

Physiologic Change in Hypoglycemia in Diabetes Patients in Rajavithi Hospital Using Non-Invasive Hypoglycemic Warning Wearable Devices: A Pilot Study

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Abstract

Background: Hypoglycemic events are serious side effects which can occur when intensive glycemic control is being used to prevent vascular complications in diabetic patients. A wearable device which warns of impending hypoglycemia may help to achieve better control of diabetes. ***Objective:*** To identify physiologic changes during hypoglycemic events in diabetic patients using a wearable device. ***Materials and Methods:*** This was a pilot study of 28 glycemic events from 10 participants who used wearable hypoglycemic devices with Continuous Glucose Monitors (CGMs) in order to confirm hypoglycemic events during the study period. Variations in skin body temperature, pulse rate and skin resistance were also analysed. Data from the wearable hypoglycemic devices were collected and compared with those from CGMs to find significant variables during the hypoglycemic events. ***Results:*** Decrement of body temperature (Min BT-Mode BT) was greater in the hypoglycemic event group (-1.73±2.07 compared to -0.07±0.51in the non-hypoglycemic event group). Increment of heart rate (Max HR-Mode HR) was also higher in the hypoglycemic event group at 30.57±22.08 compared to 13.79±20.04. Decrement of skin resistance (Min SR-Mode SR) was -50.89±44.95 in hypoglycemic event group compared to -7.47±22.60 in non-hypoglycemic event group. All these physiologic changes were statistically significant with p-values= 0.015, 0.046 and 0.002 respectively. ***Conclusion:*** This is the first time a scoring system for hypoglycemic response from wearable devices has been used in Rajavithi Hospital.

Keywords: ***Hypoglycemia, Wearable device, Diabetes Mellitus***

Introduction

Results of the Diabetes Control and Complication Trial (DCCT) Research group [1] and The UK Prospective Diabetes Study (UKPDS) [2] showed, at the end of the initial trials, that intensive glycemic control significantly lowered the risk of microvascular complications (retinopathy and nephropathy) and follow-up trials [3,4] showed that it also lowered the risk of macrovascular problems and mortality. Physicians attempted to control their patients' diabetes using intensive glycemic control to prevent diabetic complications; however, later diabetes landmark studies added more information about long-standing diabetes (with a duration of over 10 years) treated with more aggressive glycemic controls, and it was discovered that this treatment caused increased mortality rates when hypoglycemia occurred during the study [5].

Hypoglycemic events in diabetes are serious side effects of intensive treatment aimed at maintaining glycemic levels in order to target HbA1c and prevent microvascular and macrovascular events, especially major cardiovascular complications. Symptoms of hypoglycemia mostly originate from the autonomous central nervous system (autonomic response) e.g. tachycardia, sweating and a decrease in body temperature, often referred to as a "cold sweat". Non-invasive wearable devices for hypoglycemia were invented to provide an early-warning system capable of predicting hypoglycemic events which could then be analyzed with CGM devices and confirmed with capillary blood glucose during hypoglycemia monitoring.

Non-invasive hypoglycemic warning devices for diabetes have been developed to detect hypoglycemic signs such as decreased body temperature, increased heart rate and sweating using biosensors which monitor skin temperature (°C), heart rate (beats per minute) and skin resistance (kilo-Ohms; kΩ). This novel monitoring system for diabetes patients continuously records information via a cellular network and stores it in a cloud and web server system. The battery-powered device consists of a set of three skin biosensor electrodes for the measurement of physiological

parameters, and the sensors are composed of conductive polymer-based material which has low impedance and low noise characteristics. This device is designed as a wearable watch arm–belt in contact with skin around the arm to monitor and record study parameters during hypoglycemia using CGMs and self-monitoring blood glucose (SMBG) together with capillary blood glucose.

Materials and Methods

We studied 70 participants (T1DM=31, Control=39) in a 3-month pilot study. There were no signs of late diabetes complications or other comorbidity disease. The five T1DM patients were on insulin therapy prescribed by their physicians. Their average insulin dose was 34.54 units per day, their mean blood glucose level was 32.12 mg/dl, average glycosylated hemoglobin (HbA1c) was 6.71%, and their average age was 34.54 years-old.

Participants were given an appointment to attend the medicine out-patient department (OPD) in Rajavithi Hospital in the afternoon to have CGMs and hypoglycemic warning wearable devices fitted. After they had given informed consent, we fitted CGMs to monitor their extracellular fluid glucose with wearable devices for 5 to 7 days at their homes. Data from the CGMs and wearable devices were recorded every 5 minutes during the study, and the CGMs and wearable devices were removed on the follow-up day.

Analysis was performed with SPSS version 17.0 (SPSS, Chicago, IL, USA). Biosensor parameters from hypoglycemic events were analyzed by matched time-stamp with the wearable devices and CGMs at hypoglycemic times. Data were presented as mean ± standard deviation (SD) or median (range) for continuous variables and number (%) for categorical variables. Differences in the frequencies of events between groups were analyzed using chi-square test or Fisher's exact test. Student t-test or Mann-Whitney test were used to compare continuous variables between groups. The physiologic change parameters from the monitored data were the changes between mode and minimum/maximum data during hypoglycemic events. A p-value of less than 0.05 was considered significant. This study was approved by the ethics committee of Rajavithi Hospital.

Results

The general demographic data of our study such as age, female sex percentage and percentage of night–time hypoglycemia were not significantly different in the hypoglycemic and non-hypoglycemic event groups during monitoring of hypoglycemia with CGMs and SMBG as shown in table 1. We found that the average percentage of hypoglycemia duration during the day was 9.12±4.12% in the hypoglycemic event group which was significantly higher than in the non-hypoglycemic event group (only 1.91±4.04%) with p-value <0.001. Average blood glucose during CGMs, average glycosylated hemoglobin A1c and total dose of insulin per day were significantly higher in the hypoglycemic event group with p-value = 0.024, 0.004 and <0.001 respectively as shown in table 1.

Table1. General demographic data of hypoglycemic and non-hypoglycemic event groups with CGMs and wearable devices

Demographic Data	Hypoglycemic event(n=31)	None-hypoglycemic event(n=39)	p-value
Age(yrs)	32.87±7.97	37.18±6.91	0.149
Female sex(%)	45.55	37.50	0.657
Night-time hypoglycemia (%)	41.16	9.09	0.274
Time for hypoglycemia of the day (%)	9.12±4.12	1.91±4.04	<0.001
Average blood glucose during CGMS monitoring(mg/dl)	157.76±50.87	115.73±34.32	0.024
Average HbA1c during CGMS monitoring (%)	7.34±1.76	5.75±0.96	0.004
Total insulin dose during CGMS monitoring(unit)	44.87±9.55	10.22±17.68	<0.001

Changes in physiologic response were monitored during hypoglycemia, and the pattern of hypoglycemia was recorded in relation to the parameters of interest, such as body temperature, heart rate and skin resistance, using data from the wearable devices as shown in figure 1. We found that body temperature was the best parameter for identifying hypoglycemic patterns with a 100% occurrence, while increased heart rate was found in 82.35% of hypoglycemic events, and decreased skin resistance was found in only 52.9% of the hypoglycemic pattern. All parameters of interest (body temperature, heart rate, skin resistance and overall parameter) were strongly statistically significant in the hypoglycemic event group compared with the non-hypoglycemic event group with p-values of <0.001, <0.001, 0.004 and <0.001 respectively, as shown in table 2. Minimum response(min), Maximum response(max) and Mode(mode) when hypoglycemia were not statistically significantly different in body temperature; we found only Maximum(max) heart rate response and Minimum(min) skin resistance response during hypoglycemia were statistically significant with p-value = 0.035 and 0.009 as shown in Table 2.

Table2: Comparison of physiologic response change and hypoglycemic-compatible patterns in hypoglycemic and non-hypoglycemic response events

Compatible pattern	Physiologic data for hypoglycemic response compare with non-hypoglycemic event			% Compatible time with hypoglycemia event	P-Value for compatible pattern for hypoglycemia
	Min	Max	Mode		
Body Temperature pattern for hypoglycaemia	31.33±2.52 p value=NS	34.98±2.81 p value=NS	33.06±1.97 p value=NS	100%	<0.01
Heart rate pattern for hypoglycemia	74.43±8.18 p value=NS	115.14±30.43 p value=0.035	84.36±14.52 P value = NS	82.35%	<001
Skin resistance pattern for hypoglycemia	35.22±29.52 P value = 0.009	92.89±21.33 P value= NS	92.78±21.67 P value = NS	52.94%	0.004
Overall pattern for hypoglycemia	-	-	-	94.12%	<0.001

Response change during hypoglycemia monitoring using wearable devices showed that decrement of body temperature (Min BT-Mode BT) was greater in the hypoglycemic event group (-1.73±2.07 compared to -0.07±0.51 in the other group); increment of heart rate (Max HR-Mode HR) was also higher in the hypoglycemic event group at 30.57±22.08 vs. 13.79±20.04 in non-hypoglycemic events; and decrement of skin resistance (Min SR-Mode SR) was -50.89±44.95 in the hypoglycemic event group vs. -7.47±22.60 in non-hypoglycemic events. All of these physiologic changes showed statistical significance with p-values = 0.015, 0.046 and 0.002 respectively, as displayed in Table 3. ROC analysis of all parameter changes is shown in Figure 2.

Table 3: Compatible physiologic change during hypoglycemic events using hypoglycemic wearable devices

Compatible physiologic change for hypoglycemic event	Change of compatible parametes		P-Value
	Hypoglycemic	Non-hypoglycemic	
Body temperature compatible value for hypoglycemic pattern (Min BT – Mode BT)	-1.73±2.07	-0.07±51	0.015
Heart rate compatible value for hypoglycemic pattern (Max HR – Mode HR)	30.57±22.08	13.79±20.04	0.046
Skin resistance value for hypoglycemic pattern (Min SR-Mode SR)	-50.89±44.95	-7.47±22.60	0.002

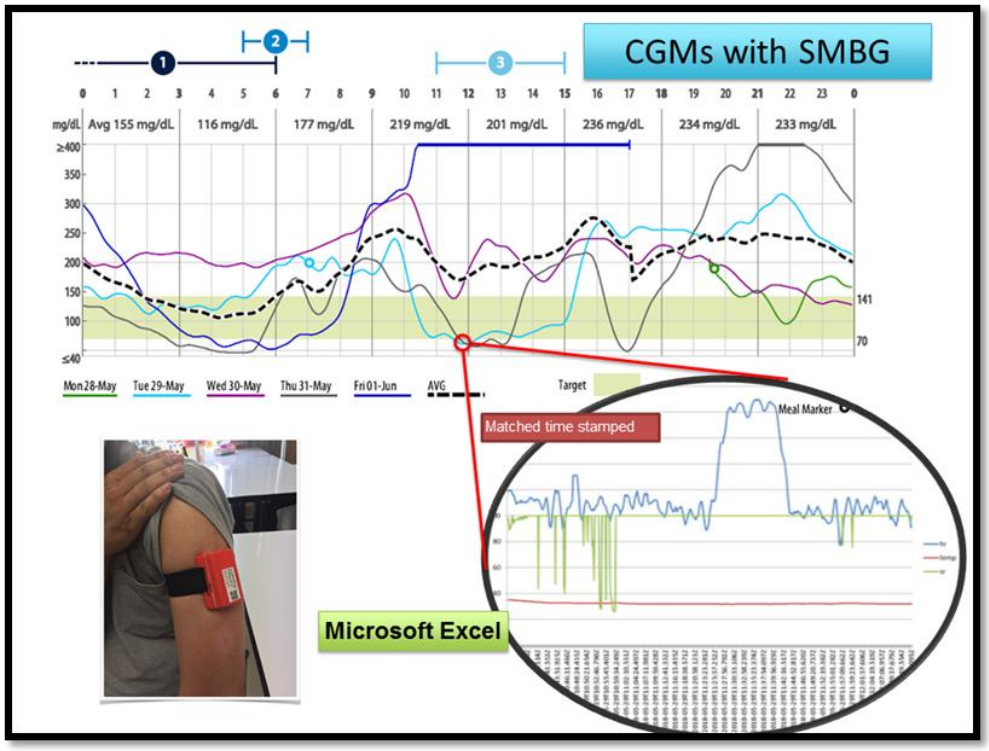
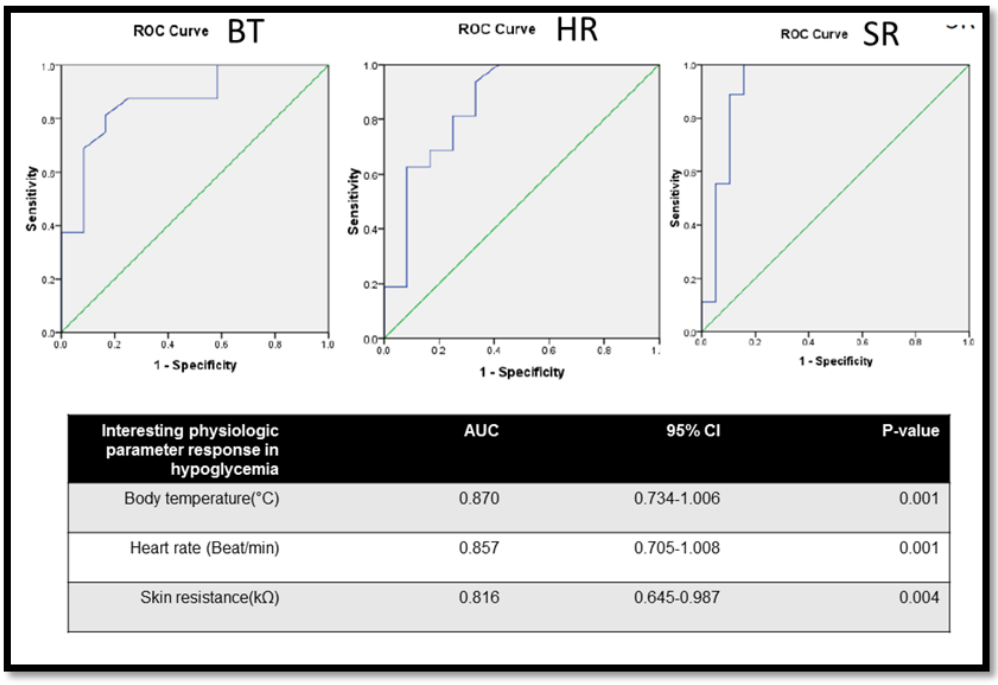


Figure 1: Matching hypoglycemic time between CGMs and Microsoft Excel to determine hypoglycemic pattern from wearable devices.



Interesting physiologic parameter response in hypoglycemia	AUC	95% CI	P-value
Body temperature(°C)	0.870	0.734-1.006	0.001
Heart rate (Beat/min)	0.857	0.705-1.008	0.001
Skin resistance(kΩ)	0.816	0.645-0.987	0.004

Figure 2: ROC curve of compatible parameters for hypoglycemia events during CGMs and SMBG (BT: Body temperature, HR: Heart Rate, SR: Skin resistance)

Discussion

Severe hypoglycemic events which can result from intensive diabetes control constitute a very serious concern for healthcare providers who monitor their patients to achieve better control. They are especially dangerous for people who cannot call for help during hypoglycemic events, such as extremely elderly patients, those with cerebrovascular disease, and other vulnerable groups, based on research conducted prior to our study (unpublished data). These are significant factors during severe hypoglycemia, especially for those of advanced age with insulin usage dose and medication usage such as sulfonylurea.

Hypoglycemic episodes in diabetes can be detected non-invasively, continuously and effectively from the record-time physiological responses measured via wearable devices used at Rajavithi Hospital. We found body temperature response from the wearable devices was the most valid indicator in hypoglycemia monitoring. Although heart rate and skin resistance were able to detect hypoglycemia, they were less reliable than body temperature response. If we combine all response parameters, we can detect hypoglycemia with a detection pattern as shown in Table 2 with 94.2% compatibility with hypoglycemia, which is statistically significant ($p<0.001$). This study showed a novel physiologic response during hypoglycemia, while a prior study found a significant increase in motor activity detectable by actigraphy during periods of autonomic nocturnal hypoglycemia. Actigraphy has so far been successfully used for analysis of pathological sleep in adults [7,8].

Unlike the "Hypomon study" [9], our study did not show warning algorithms for hypoglycemia from physiologic change. In the Hypomon study design, participants were asked to follow their normal diet, exercise/activity, and insulin routines for the day of the study. Upon arrival at the hospital, data were collected from the subjects, including demographic information and a finger-prick (capillary) BG level. The participants were then cannulated by the clinical research nurse for venous blood sampling throughout the night. Participants were supervised by the nursing staff (with a ratio of participants to nurses of at most 3:2). The Hypomon study results from nocturnal hypoglycemia found sensitivity of 73% (8/11), specificity of 68% (28/41), positive predictive value of 38%, and negative predictive value of 90% using their warning system; in contrast, our study monitored all physiologic change through the day time while patients were wearing the wearable devices, and our results can be applied in home monitoring methods in real-life situations.

In further studies, the next generation of wearable devices will be designed to emit a warning sound and will have motor movement sensors during hypoglycemia to construct a better algorithm for predicting hypoglycemia, Artificial Intelligence (AI) should be utilized to improve the precision of non-invasive hypoglycemia warning wearable devices. Findings could be applied in intensive care of diabetes patients and be part of the healthcare policy for the Non-Communicable Disease (NCD) service plan of our country.

Conclusion

This is the first study of physiologic response in hypoglycemia using non-invasive wearable devices to monitor hypoglycemic events throughout the day in real-life situations. Our data can be useful in further studies for setting warning systems in future non-invasive wearable hypoglycemic warning devices.

Ethics approval and consent to participant

This protocol was approved by Rajavithi Hospital Ethic committees

Conflict of interest:

No conflict of interest

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