Investigating the Efficacy of Using Hand Tremors for Early Detection of Hypoglycemic Events: A Scoping Literature Review

Diabetes is a prevalent condition affecting millions of patients globally. Some diabetic patients suffer from a deadly condition called Hypoglycemia (sudden drop in blood glucose levels). Continuous Glucose Monitors (CGMs) have been the most pervasive tool used to track blood glucose levels but these tools are invasive and costly. While early detection of hypoglycemia has been studied, current approaches do not leverage tremors; which are a primary symptom of hypoglycemia. A scoping review was conducted to understand the relationship between tremors and hypoglycemia, and to document any efforts that utilized tremor signatures non-invasively to detect hypoglycemic events. Findings suggest that hypoglycemic tremors are a medium frequency tremor, more resistant to hypoglycemic impairment than other symptoms, and have not been fully explored yet. This paper also documents the work in progress to utilize a novel wearable device that predicts the onsets of hypoglycemia using hand tremor sensing.

INTRODUCTION

With the continuous growth in the number of people living with diabetes, currently at 415 million globally and expected to exceed 642 million by 2040 (Diabetes Prevalence, 2015), research has been trying to find better ways to help patients manage their symptoms. One of the greatest dangers of diabetes is a condition called hypoglycemia, which occurs when the blood glucose (BG) level drops below Level 1 of 70mg/dL (3.9mmol/L). If the BG level drops below 54mg/dL (3.0mmol/L), it can be categorized as Level 2 which is a serious condition threatening the patient's life, and might require external intervention if not addressed by the patient in a timely manner (American Diabetes Association, 2016).

Hypoglycemia has been associated with several salient symptoms including drowsiness, tremors, sweating, and nervousness (Mühlhauser et al., 1991). Hypoglycemia can generally be attributed to insufficient food consumption, incorrect insulin dosage, physical exercise, among other reasons (Gama, Teale, & Marks, 2003). For people living with diabetes, the fear of hypoglycemia is a debilitating worry on a daily basis. In an online survey, 45% of respondents noted that they withdrew from exercising, and 15% suffered a vehicle injury because of their condition (Weitzman et al., 2013). Nocturnal hypoglycemia is especially concerning since it happens during the night time and could result in a condition known as "dead in bed", whereby patients are unable to wake up to stabilize their blood sugar (e.g., by consuming snacks). It is noteworthy that around three quarters of the hypoglycemic episodes that were detected in one experiment occurred during the night time (Unger & Parkin, 2011).

Currently, continuous glucose monitoring devices (CGMs) are the most popular devices in the market that monitor the BG level of patients with Type 1 diabetes mellitus (T1DM) and alert the user when their glucose levels are suboptimal. CGMs have been shown to positively affect the quality of life by improving patients' perceived control over diabetes and hypoglycemic safety (Polonsky & Hessler, 2013). While CGMs have shown promise to detect low glucose levels during the day (Mastrototaro et al., 2008), devices have been less accurate when tested at night (Bay et al., 2013). In addition, the most popular CGMs are invasive, not commonly prescribed for people with type 2 diabetes mellitus (T2DM), require frequent calibration (Facchinetti, 2016), and are costly, which prevents many potential users from adopting this technology. In fact, only 38% of the respondents in an online survey reported that they used CGMs even though 88% of the participants had T1DM (Weitzman et al., 2013). In another study, 44% of CGM users (2/3 with some college education) in the United States reported that they were not satisfied with the cost of CGMs (Polonsky & Hessler, 2013).

While other hypoglycemia detection technologies exist, these tools use sweating and body temperature (Harris et al., 1996), which are relatively difficult to monitor or are affected by environmental constraints (e.g., heat/cold, movement). Few studies have leveraged tremors in device or technology designs as signatures of low blood glucose levels, despite being a key symptom of hypoglycemia. The objective of this research is to investigate an affordable, non-invasive and wearable solution that utilizes information about tremors to detect hypoglycemic events and to improve diabetes management. Such technology may facilitate access to an affordable solution which will serve the underprivileged communities and less advanced nations. This paper aims to document the findings from a scoping literature review that focuses on attempts made at detecting hypoglycemia onsets in a non-invasive manner, and explore the relationship between tremors and hypoglycemia. This paper also presents our preliminary user-centered design and evaluation approach.

METHOD

A scoping literature review was performed to understand the linkage between tremors and the onset of hypoglycemia. The keywords ["hypoglycemia"] and ["tremor" OR "trembling"] were searched in MEDLINE and Compendex on October 18, 2017. The initial search yielded 78 results. An additional search with search terms ["hypoglycemia"] and ["non-invasive"] was conducted on the same databases, but did not yield any additional studies that looked at tremors. Only studies published in English that have looked at the relationship between hypoglycemia and tremors were included. Studies were excluded if they were based on an invasive technology.

RESULTS

After removing the duplicates and applying the exclusion criteria, only 9 studies were found to be relevant to hypoglycemic tremors but only a few documented tools or technologies utilizing tremor as a diagnostic metric. In what follows we summarize these studies as well as several other studies that investigated hypoglycemia detection using other (non-tremor) physiological metrics.

Tremor Symptoms

Tremor associated with hypoglycemia has been categorized as enhanced physiological tremor at a medium frequency (Rana & Chou, 2015). However, very few studies have leveraged hypoglycemic tremors to detect hypoglycemia, even though they are very common among patients with diabetes. In a study conducted by Mühlhauser et al., (1991), 17% of the 247 teenage patients treated with animal insulin preparations, and 19% of the 276 patients treated with human insulin reported that "trembling" was the first symptom they recognized that indicated the onset of hypoglycemia. Berlin et al. (2005) surveyed 241 participants (age 19-78 years) with either diabetes types; 77.5% of the respondents who reported they were hypoglycemic aware, affirmed that they have tremor symptoms, and 57.6% of those who claimed to be impaired stated that they also get tremors. In another survey, 74% of 40 children (10.1 ± 6.2 years) with diabetes surveyed attested that trembling is a frequent symptom they notice (Chiarelli et al., 1998).

Among the few studies focusing at tremors, Schechter et al., (2012) utilized a set of 4 sensors around the wrist on patients with T1DM to monitor nocturnal hypoglycemic events. The factors considered were heart rate, perspiration, skin temperature, and tremors. Actigraphy was utilized to detect hand tremors but tremor detection was only based on any continuous time span >30s with movement. They did have high accuracy when compared to CGMs over a total of 22 nights for 10 teenage participants . However, they used a small sample size, investigated the effects of tremors in combination with other symptoms not in isolation, and did not explicitly measure the frequency of the tremor.

Heller et al., (1987) reported that participants in their study who claimed they were hypoglycemia aware, had a noticeable increase in tremor readings when the BG dropped to 2.5mmol/L. Later, George et al., (1995) manipulated the BG level for 8 participants and found that when it dropped from 5mmol/L to 2.5mmol/L, tremor symptoms were noticeable. This was objectively assessed by a ring accelerometer that measured the increase in tremor in the index finger by calculating the root mean square (RMS) voltage over a 1 minute period.

Non-invasive Approaches to Detect Hypoglycemia

Several attempts have been made to detect hypoglycemia through various physiological changes in the body. Electroencephalography (EEG) signals from the brain have been explored, and the alfa frequency was found to differ significantly during nocturnal hypoglycemia (Nguyen & Jones, 2010). A glucose clamp experiment on 5 children found that EEG parameters are highly correlated with the condition of the patients (Nguyen et al., 2013). However, the data processing was not done in real time and was limited in the sample size tested. Electrocardiography (ECG) signals have also been analyzed in order to detect hypoglycemic episodes with the idea that longer QT intervals increase the risk of hypoglycemia. Using deep learning, one study was able to detect hypoglycemic events in 15 children with T1DM at a sensitivity of 80% values (San, Ling, & Nguyen, 2016).

Hypoglycemic detection through the use of a biosensors based on optical chirality have shown promise (Varadan, Whitchurch, & Sarukesi, 2003) but follow up validation studies are largely absent. Another study found a strong correlation between BG levels and millimeter wave absorption (MMW) whenever hypoglycemia was induced (Siegel, Lee, & Pikov, 2014). While several other studies focused on non–invasive monitoring glucose levels, an exhaustive review of these methods is beyond the scope of this short article (see Howsmon & Bequette, 2015 for a detailed review). For example, a new and relatively accurate biosensor has shown promise when tested on 20 T1DM subjects (Zanon et al., 2017). Spectroscopy methods have also been used but found to require much more improvement in order to match up to the accuracy offered by popular CGMs on the market (Yadav, Rani, Singh, & Murari, 2015).

Several studies also monitored multiple symptoms of hypoglycemia to increase accuracy of detecting hypoglycemia episodes. Yotha et al., (2016) configured a device based on 3 sensors that looked at variations of pulse rates, humidity, and temperature of the skin around the wrist to render a 3-level hypoglycemia risk. Harris et al. (1996) monitored pulsatile changes in blood flow, internal pulse, body temp, and skin conductance.

Accounting for Hypoglycemic Unawareness

Research shows that recurrent hypoglycemia events decrease the patient's awareness of its occurrence over time causing their symptoms to be impaired regardless of the type of diabetes (Berlin et al., 2005). Mühlhauser et al., (1991) found that approximately 17% and 18% of the patients treated with animal insulin and human insulin respectively reported being unaware of their symptoms. Teuscher & Berger also found that 36% of their insulin-dependent diabetes mellitus (IDDM) patients with hypoglycemia symptoms reported a decrease in their tremor and sweating symptoms when moved from bovine/porcine insulin to human insulin, making them less hypoglycemia aware (Teuscher & Berger, 1987). Age, smoking, and having T2DM were found to increase the possibility of impaired hypoglycemia awareness as compared to T1DM (Berlin et al., 2005). In addition, alcohol was found to suppress the symptoms of T1DM (Kerr et al., 1990). However, the reduction in sweat and adrenaline responses in hypoglycemia has been found to be significant over time and no significant reduction was reported in the finger tremor readings (George et al., 1995).

DISCUSSION

A scoping review was conducted to uncover the gaps and opportunities in the literature on attempts to utilize hypoglycemic tremors for the detection of hypoglycemia. Findings suggest that while many studies attempted to detect this condition through other physiological changes, very few have focused on tremor. In addition, only few studies rendered commercially available technologies. Furthermore, impairment of hypoglycemic symptoms is not carefully accounted for in most studies.

Hypoglycemia Detection through Tremors

Our findings suggest that tremor symptoms do not become impaired in the same manner that skin conductance and adrenaline responses do with hypoglycemic unawareness (George et al., 1995). Given that recurrent hypoglycemic episodes increase the risk of death by at least 3 folds (McCoy et al., 2012), it is vital that patients with diabetes properly recognize its early onset and act accordingly. The literature shows that patients with either type of diabetes could have reduced hypoglycemia awareness due to several factors.

It seems also that few studies that have attempted to detect tremors either considered them as any movement for a specific time (Schechter et al., 2012) or in terms of increased RMS voltage (George et al., 1995) without studying the frequency of that tremor. This leads us to believe that tremor detection is worth investigating in order to better understand and prove that it can predict the onset of hypoglycemia. This is further motivated by the fact that the tremor accompanying hypoglycemia is categorized as enhanced physiological tremor (Rana & Chou, 2015; Lyons et al., 2008); a medium frequency tremor as compared to Parkinson Disease (PD) tremor which occurs at a lower frequency. Enhanced physiological tremor is likely to happen in the hands and is bilateral and symmetric (Rana & Chou, 2015). It is worth noting that neurologic symptoms might be more common in older patients and confused with other age-specific conditions (Jaap et al., 1998), which is why testing the tremor frequency band is important.

Actigraphy has been used to test the signal characteristics of various neurologic conditions such as Parkinson's Disease (Van Someren et al., 2006) and can be utilized with hypoglycemic tremors. Work is in progress to design a wearable sensor that analyzes the tremor signals automatically and in real-time, in addition to a mobile application that communicates with the sensor and provides extra features aimed at helping the patients manage their diabetes. Since hypoglycemic tremors are reported to be of higher frequency than PD tremors, a wearable sensor to detect this symptom either on the finger, the wrist, or both is being assessed. In what follows we first discus current tremor sensor technologies and then discuss some human factors considerations for the design of a proposed wearable technology.

Current Non-Invasive Commercialized Technologies

Many studies on wearable sensors performed in a clinical setting have not been able to move into the market because they were not robust enough (Mukhopadhyay, 2015). Among devices aimed at non-invasively detecting hypoglycemia, the GlucoWatch® G2 (Animas Corp - West Chester, PA) and HypoMon® (AiMedics Pty Ltd – Sydney, Australia) that were promoted at one point, had been discontinued from the market due to high false alarms ("Animas Glucowatch", n.d.; "Hypomon Sleep-time", 2013). This has left Diabetes Sentry (Diabetes Sentry – Fort Worth, TX) as the only non-invasive technology to automatically detect hypoglycemia ("Diabetes Sentry", n.d.).

An upcoming technology called Glucowise^{TM} (MediWise - London, United Kingdom) uses high frequency waves to approximate BG level ("Gluco-Wise", n.d.). The K'Watch Glucose (PK Vitality – Paris, France) also anticipated this year uses a biosensor that approximates glucose levels based on the interstitial fluid below the skin's surface, however similar to the GlucoWise^{TM}, they both need to be manually triggered to measure the BG level ("K'Watch", 2017). There might be other technologies that are invasive or primarily concerned with continuous glucose monitoring and hence not discussed here.

Human Factors Considerations for a Wearable Tremor-based Hypoglycemia Detection Technology

Since tremors appear to be a valid indicator of hypoglycemia, a wearable sensor will be assessed at detecting clamp-induced hypoglycemia in a controlled environment. The wearable sensor will attempt to confirm the unique frequency band of hand tremors, test out the concept at different position the wrist and fingers could be in, and assess the accuracy of such a setup.

Recent studies note limited assessment of the usability of non-invasive continuous glucose monitoring devices and that there are still many challenges in their accuracy and usability (Lin et al., 2017). In addition, another challenge for wearable devices has been maintaining user engagement beyond just usability (Mukhopadhyay, 2015). Therefore, a human-centered design will be used to solicit needs, expectations, and user requirements and inject this feedback systematically into the design and development cycle.

Usability and Wearability. One of the main benefits of using tremoer-based sensors is the non-invasiveness which renders less risk to the body. Further, wearable sensors based on actigraphy generally require no maintenance or changeable parts while several technologies that continuously monitor glucose (e.g. Dexcom G5®) require replacement parts to be changed often, which puts a recurring cost on the patient. Calibration has also been deemed to be a setback of continuous glucose monitors (Facchinetti, 2016); an issue not expected to occur with the proposed system. Some technologies might also have varying calibration settings and accuracy results based on user demographics (Lin et al., 2017); a consideration which will be taken into account during iterative formative usability testing phase.

Among the other advantages would be having the device worn on the wrist which increases its "wearability", as it can be designed to look like a watch, and not interfere with daily activities. Our design would have to account for the tradeoff between data processing, sensor size, and battery life to find the optimal balance. Also, the device will generally serve as an early reminder for the patient when their blood level is in the 60-69 mg/dL range at which the initial symptoms are commonly reported (Weitzman et al., 2013), and as an alarm when the patient is asleep and nocturnal hypoglycemia happens. As previously mentioned, the device can be used by patients with either type of diabetes as both types have complained of tremor symptoms (Berlin et al., 2005).

Once the concept is proven, inaccurate predictions are anticipated to be lower since tremor frequency is reported to occur in a designated frequency band upon the onset of hypoglycemia. Meanwhile, other technologies based on skin conductance and body temperature have been shown to give inaccurate results (Howsmon & Bequette, 2015), mainly because of their susceptibility to environmental factors. As shown before, tremors are less prone to becoming impaired compared to other symptoms. Lastly, a mobile application will supplement the device and provide various features that aid in the day to day management of diabetes.

mHealth and User Engagement. The rise of mobile health "mhealth" has offered mobile applications that help patients manage diabetes symptoms. Mobile applications can assist to log food and insulin intake, glucose readings, and process data in real time, plus educate the user about their condition (Conway et al., 2016). After optimizing usability and functionality, the next challenge is getting users to adhere to the use of a particular technology. In the realm of managing diabetes and improving glycemic control, self-management has been shown to be very important (Norris et al., 2002). Even before the spread of interactive apps, the simple use of phone messaging has been shown to improve HbA1c values as well as patient self-efficacy (Holtz & Lauckner, 2012).

However, the literature has also shown that the features in most apps do not meet user preferences (Conway et al., 2016) and that few theories of engagement have actually been implemented in practice; Showing a disconnect between app developers and the theoretical research (Sama et al., 2014). Apps surveyed in one study found that 100% of diabetes management apps had a glucose level log, followed by 76% having graphic analysis, while 42% had an insulin logger and only 14% had an educational feature among others (Conway et al., 2016). Another study found that only one third of the individuals across common chronic conditions - including diabetes - agreed that health apps have the ability to dramatically improve health. Consequently, healthy individuals were found to be significantly more likely to download such apps and engage with them (Robbins et al., 2017). This highlights the need to utilize the findings from the field of user engagement and persuasive technologies in the design of a mobile application that seeks to improve the functionality of the proposed wearable device.

CONCLUSION

Alternative technologies to continuous glucose monitors might not completely be able to replace them, but given the significant amount of people who are unsatisfied with the costs and usability of CGMs, investigating more affordable approaches is timely. In addition, CGMs have significant other setbacks for the detection of hypoglycemia. Most importantly, they are invasive, bring the hassle of regular calibration, and are limited to T1DM patients. With the advancements in understanding and sensing the physiological changes in the body at low blood sugar levels, there have been several studies seeking an alternative route to non-invasively detect hypoglycemia. Since tremors have been shown to occur for all patients with diabetes - even those with impaired hypoglycemia awareness - and are categorized as medium frequency tremors, work is in progress to prove the concept of detecting hypoglycemia through its associated tremors. This would offer an affordable technology anticipated to give more accurate predictions than other non-intrusive devices in the market. With that in consideration, human factors considerations influencing sustained user engagement must be accounted for throughout the design and implementation of such a device so that it may help patients assume better control of the technology, and give better satisfaction in the management of hypoglycemia.

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