NOCTURNAL HYPOGLYCEMIA PREDICTION IN DIABETIC CHILDREN PARTICIPATING IN A SPORTS DAY CAMP - FIRST RESULTS

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ABSTRACT

Nocturnal hypoglycemia is frequent in children with type 1 diabetes (T1D), daytime physical activity being the most important risk factor. The risk for late postexercise hypoglycemia depends on various factors and is difficult to anticipate. The availability of continuous glucose monitoring (CGM) enabled the development of various machine learning approaches for nocturnal hypoglycemia prediction for different prediction horizons. Studies focusing on nocturnal hypoglycemia prediction in children are scarce, and none, to the authors' best knowledge, investigate the effect of previous physical activity. In this work, continuous glucose and physiological data from a sports day camp for children with T1D were input for logistic regression, random forest, and deep neural network models. Results were evaluated using the F2 score, adding more weight to misclassifications as false negatives. Data of 13 children (4 female, mean age 11.3 years) were analyzed. Nocturnal hypoglycemia occurred in 18 of a total included 66 nights. Random forest achieved best results for nocturnal hypoglycemia prediction. Predicting the risk of nocturnal hypoglycemia for the upcoming night at bedtime is clinically highly relevant, as it allows appropriate actions to be taken - to lighten the burden for children with T1D and their families.

1 INTRODUCTION

Type 1 Diabetes (T1D) affects more than 8 million people worldwide, 1.5 million of them being younger than 20 years of age (Gregory et al., 2022; Patterson et al., 2019). Low blood sugar (hypoglycemia) is the most feared and common acute complication of T1D (Nordfeldt & Ludvigsson, 2005; Glocker et al., 2022), and the constant risk of hypoglycemia represents a great burden, in particular for children and their caregivers (Patton et al., 2020). Asymptomatic nocturnal hypoglycemia is frequent, and episodes often are prolonged for several hours with the most important risk factor being physical activity during the day (Bachmann et al., 2016; Jaggers et al., 2019).

With the current state of knowledge, it is challenging to provide the correct personalized recommendations to prevent exercise-associated hypoglycemia, in particular, late-onset post-exercise hypoglycemia. Developing preventive measures to avoid such nocturnal hypoglycemia would be desirable and could increase the children's safety overnight and quality of life of the children and caregivers.

Studies focusing on nocturnal hypoglycemia prediction in children are scarce (Dave et al., 2021; Duckworth et al., 2022; Sampath et al., 2016; Klimontov & Myakina, 2017). In two studies, noctur-

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nal hypoglycemia could be predicted with good sensitivity, thus only over max. 60 min and not in the context of physical activity (Dave et al., 2021; Duckworth et al., 2022).

In this study, we focus on predicting nocturnal hypoglycemia in children with T1D using continuous glucose monitoring (CGM) and physiological data acquired during day and night. We incorporate the children's particularities like longer sleep duration, focusing on the entire night (prediction horizon of 9 hours), or investigating the effect of previous physical activity. Second, as the children performed various structured physical activities during the day in the dataset that we are considering, we want to analyze if including data from a wearable device improves the outcomes. Third, as more advanced machine learning techniques such as deep learning are currently underrepresented in literature, we want to investigate the performances of Deep Neural Network (DNN) models like Recurrent Neural Networks (RNNs) and Multilayer Perceptron (MLP) compared to the most used approaches in literature like logistic regression and random forest.

2 METHODS

2.1 DATA

Data of children with T1D participating in a one-week sports day camp were considered (Marx et al., 2023). Additionally, to CGM devices, the children were equipped with a physiological wearable sensor (Everion, Biofourmis, Boston, US).

Hardware The hardware consisted of a glucose sensor (intermittently scanned continuous glucose monitoring (isCGM), Freestyle libre 2 (Abbott Diabetes Care Inc., Alameda, US) or a CGM, Dexcom (Dexcom, San Diego, US) or Guardian 3 (Minimed Medtronic, Northridge, US)) and a physiological wearable sensor (Everion, Biofourmis, Boston, US). The glucose data were saved every $5\,\mathrm{min}$ (CGM) or every $15\,\mathrm{min}$ (isCGM). The glucose measurements were completed with self-monitoring blood glucose (SMBG) that were manually noted in a logbook. Additionally to sensor glucose measurements, SMBG were performed hourly during exercise sessions, in each case of symptoms of hypoglycemia, and in case of sensor glucose values below $3.9\,\mathrm{mmol/l}$ or above $15\,\mathrm{mmol/l}$. The Everion sensor is a CE-certified research device and captured 22 vital signs in real-time. Additionally, an associated quality measure was available for seven vital signs. In this work, we selected ten vital signs—and their associated quality measures, if available—for further processing. The ten vital signs were Activity classification, Blood pulse wave, Core temperature, Galvanic Skin Response electrode, Heart rate, Heart rate variability, Motion activity, Number of steps, Perfusion index, and Respiration rate. The sampling rate of the vital signs was $1\,\mathrm{Hz}$. The Everion sensor was attached to the upper arm (right or left) with an appropriately sized armband.

Participants 17 children with T1D were recruited for the study. Inclusion criteria were T1D for at least 6 months, age 7 to 16 years, insulin treatment consisting of multiple daily injections or continuous subcutaneous insulin infusion, and written informed consent by the children and/or parents. Exclusion criteria were medication known to affect the cardiac function or repolarization, pre-existing cardiac disease, medically treated arterial hypertonia and hyopthyroidism, if not adequately substituted. The responsible Ethics Committee (Ethikkommission Nordwest- und Zentralschweiz (EKNZ), Gesuchsnummer: 2020 - 00543) approved the study.

Experimental Protocol The recruited children participated in a prospective observational study in the setting of a one-week day camp. During the day in the camp, the children were supervised by the pediatric endocrinologists. In the evenings and during the nights, the measurements and the logbook were continued at home. The first study day consisted of a trip to a climbing hall. On study days two to six, the children participated in various structured sports activities daily, divided into a $2\,\mathrm{h}$ session in the morning and one in the afternoon. Insulin doses (type, time, units), carbohydrate intake, type and duration of physical activity, and symptoms of hypoglycemia together with the SMBG were noted in a logbook by the study team.

Preprocessing Data of four children were excluded. Reasons were dropping out of the study, usage of a hybrid closed-loop insulin pump, and too sparse data available. Preprocessing was necessary for combining the glucose sensor data with the SMBG from the logbook and for the signals

of the Everion sensor. In case of two different glucose values at the same timestamp, sensor data was overwritten with SMBG and the lower glucose sensor data were kept. For data from the Everion sensor, we replaced values of duplicated timestamps with their mean. For signals with an associated quality measure, we ignored values when the quality measure was less than 50%. The activity classes of the parameter activity classification were transferred to Metabolic Equivalent of Task (MET) values (Table 2) (Ainsworth et al., 2011).

Class Definition Each night was assigned to either the class 'Nocturnal Hypoglycemia' or 'No Nocturnal Hypoglycemia'. A hypoglycemic event was defined as either 1) a single or multiple SMBG less than $3.9\,\mathrm{mmol/l}$ or 2) an interval greater than $15\,\mathrm{min}$, in which all continuous glucose measurements were less than $3.9\,\mathrm{mmol/l}$ (Dave et al., 2021; Berikov et al., 2022; Danne et al., 2017). The night as prediction horizon was defined between 10 pm to 7 am. The corresponding day was defined with the hours before the night started, between 10 am to 10 pm addressing the fact that the first study day started at 10 am.

2.2 ALGORITHM

The general idea of this work was to develop a classification system to answer the research question whether nocturnal hypoglycemia can be predicted with physiological and glucose data collected during the day.

Data Sources We used glucose measurements, the logbook, the Everion sensor, and participant information. To obtain uniform temporal data, we set the sampling interval to $5\,\mathrm{min}$ by aggregating the Everion data with the respective means. All data gaps in the glucose and the physiological data were filled with the respective mean of the corresponding data of the day. From the available participant information, the age, weight, height, BMI, and gender (male or female) were extracted to form the static data. With the available temporal and static data, four data set combinations were chosen as input data for the algorithms:
1) glucose data only, 2) glucose and static data, 3) glucose and physiological data and 4) glucose, physiological, and static data.

Baseline Models Features were engineered from the four input datasets and selected before being the input to either logistic regression or random forest. For the glucose data, we calculated eight features from literature (Berikov et al., 2022) to reflect glucose dynamics. These were coefficient of variation, lability index, low blood glucose index, $1\,\mathrm{h}$ continuous overlapping net glycemic action, minimal value, the difference between the last two values, acceleration over the last values, and linear trend coefficient (Berikov et al., 2022). In addition, we calculated time series characteristics using the Python library *tsfresh*. To reduce the number of features to the best 15 features, we conducted a performance-based, sequential feature selection using the Python library *scikit-learn*. This resulted in five different feature-data-combinations that were used for the following two baseline classifiers: 1) Logistic regression with LASSO regularization, and 2) Random forest with 10 trees. We decided to concentrate on these two classifiers as these are the most used algorithms in literature for hypoglycemia prediction (Zhang et al., 2023), and are also applied in the field of nocturnal hypoglycemia prediction (Berikov et al., 2022; Dave et al., 2021).

DNN Models The four datasets were used in the following two scenarios: 1) A RNN for the temporal data. The RNN included a masking layer followed by a bidirectional GRU (Cho et al., 2014) layer, a dropout layer, a LSTM (Hochreiter & Schmidhuber, 1997) layer, and another dropout layer. 2) A RNN for the temporal data, and a MLP for the static data. Both were combined afterward. The output of both the MLP and the RNN were concatenated and processed by an additional MLP. The RNN included a single LSTM layer. To find the best architectures, the neural networks were subject to hyperparameter optimization using the Hyperband algorithm (Li et al., 2017). We introduced class weights to the loss function during training to account for the class imbalance. We used the ReLU activation function throughout the dense layers to avoid computational complexity and vanishing gradients (He et al., 2015; Nair & Hinton, 2010). The tanh activation function was used for the recurrent layers (Chung et al., 2014; Hochreiter & Schmidhuber, 1997). We used Adam as the optimizer with a learning rate of 0.001 (Kingma & Ba, 2014; Ruder, 2016). The batch size was set

to 1 due to the small number of samples in the dataset and the intention to counteract for overfitting and poor generalization (Masters & Luschi, 2018).

Performance Measures and Evaluation The F2 score, giving more weight to sensitivity than to precision (Chinchor, 1992), was used as metric on the validation set of DNN models for stopping the training. Each machine learning model was subjected to six-fold cross-validation. In each case, 20% of the training set was subtracted to form the validation set. The shuffle and split were done in a stratified fashion so that classes were distributed almost identically among the different sets. The six-fold cross-validation approach was executed five times. Results are given as averages over the five runs, averaging the mean values and the standard deviations separately.

3 RESULTS

Data of 13 children with T1D (4 female and 9 male, age 11 $\pm$ 2 years, BMI 19.8 $\pm$ kg/m^2, Diabetes duration 4 $\pm$ 3 years, mean $\pm$ standard deviation) were used for analyzing. Of them eight children used an isCGM device and five a CGM device. 48 nights were found without nocturnal hypoglycemia and 18 with nocturnal hypoglycemia. Figure 3 shows the F2 scores for logistic regression, random forest and the deep neural network models. Figure 3 gives specificity, sensitivity, and precision averaged over the five runs.

4 DISCUSSION

The focus of this work was the prediction of nocturnal hypoglycemia in children with T1D. Different feature-data-combinations were the input for the classification task using logistic regression, random forest or DNN. Best results were obtained with time series characteristics using random forest (Figure 3). Single high values (above 80%) were reached for specificity, sensitivity, and precision for all three models. Considering that physical activity is an important risk factor for (nocturnal) hypoglycemia, we would have expected a clearer inclusion of physiological parameters to be relevant for the prediction of nocturnal hypoglycemia. It is possible that the influence of physical activity was not optimally modeled by the Everion parameters used. Improvements for future work could be targeted handcrafted features, with specific feature selection, for the Everion sensor.

Three studies from the literature (Parcerisas et al., 2022; Vehí et al., 2020; Bertachi et al., 2020) concentrated on nocturnal hypoglycemia prediction (prediction horizon of 6 h) and included wearable data. Bertachi et al. (2020) received best results (78.75% median sensitivity, 82.15% median specificity) with Support Vector Machine (SVM). Parcerisas et al. (2022) used the same dataset and achieved with SVM a median sensitivity of 74% and a median specificity of 77% for their population models. Vehí et al. (2020) used artificial neural networks and obtained a mean sensitivity of 44.0% and mean specificity of 85.9%. If we consider the differences in the studies, such as chil-

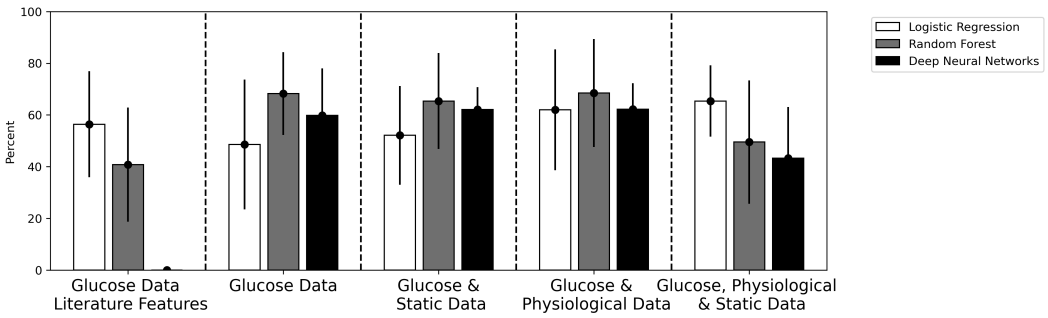

Figure 1: Mean values of the F2 scores for the overnight prediction (prediction horizon: 10 pm to 7 am) given for logistic regression, random forest and deep neural network models. The bars are calculated as mean values of the five runs. The error bars belong to the mean of the standard deviation of the five runs.

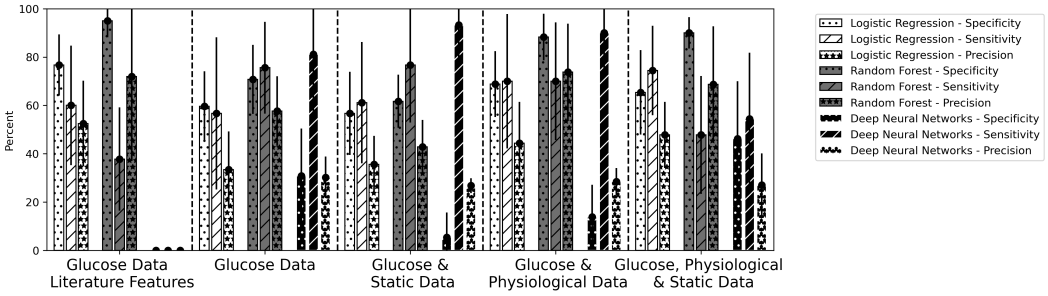

Figure 2: Mean values of Specificity, Sensitivity, and Precision for the overnight prediction (prediction horizon: 10 pm to 7 am) given for logistic regression, random forest and the deep neural network models. The bars are calculated as average values of the five runs. The error bars belong to the mean of the standard deviation of the five runs.

dren compared to adults or longer prediction horizon, we conclude that the results in this work are comparable to or even exceed the results in the literature.

We used data collected during a sports day camp. During the day, the children were supervised by pediatric endocrinologists. This study setting is less controlled than an inpatient hospitalized setting (Berikov et al., 2022; Sampath et al., 2016; Tkachenko et al., 2016). Other studies use an even less controlled outpatient setting, where participants continue their daily routines and come to the study center only at agreed times (Dave et al., 2021; Duckworth et al., 2022; Parcerisas et al., 2022; Bertachi et al., 2020). The chosen study setting allows the imitation of everyday daily life but offers opportunities for intervention and information about meals and insulin doses. Data from a less supervised setting, including a higher number of participants, will be considered in the future.

Conclusion In this work, we utilized a dataset recorded in a structured setting to assess the risk of nocturnal hypoglycemia associated with physical activity in children with T1D. In contrast to previous studies we aimed for longer-term predictions up to 9 hours (the entire night). From our point of view, the results obtained in this study are acceptable with a sensitivity of the best F2 score close to 80%. Understanding the hypoglycemia risk for the entire upcoming "critical" night is clinically relevant as it permits children and their parents to either sleep soundly or to take appropriate action such as reducing basal insulin doses, administering additional carbohydrates, or scheduling a nocturnal glucose measurement.

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