

REVIEW ARTICLE

Hypoglycaemia detection and prediction techniques: A systematic review on the latest developments

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Abstract

The main objective of diabetes control is to correct hyperglycaemia while avoiding hypoglycaemia, especially in insulin-treated patients. Fear of hypoglycaemia is a hurdle to effective correction of hyperglycaemia because it promotes under-dosing of insulin. Strategies to minimise hypoglycaemia include education and training for improved hypoglycaemia awareness and the development of technologies to allow their early detection and thus minimise their occurrence. Patients with impaired hypoglycaemia awareness would benefit the most from these technologies. The purpose of this systematic review is to review currently available or in-development technologies that support detection of hypoglycaemia or hypoglycaemia risk, and identify gaps in the research. Nanomaterial use in sensors is a promising strategy to increase the accuracy of continuous glucose monitoring devices for low glucose values. Hypoglycaemia is associated with changes on vital signs, so electrocardiogram and encephalogram could also be used to detect hypoglycaemia. Accuracy improvements through multivariable measures can make already marketed galvanic skin response devices a good noninvasive alternative. Breath volatile organic compounds can be detected by dogs and devices and alert patients at hypoglycaemia onset, while near-infrared spectroscopy can also be used as a hypoglycaemia alarms. Finally, one of the main directions of research are deep learning algorithms to analyse continuous glucose monitoring data and provide earlier and more accurate prediction of hypoglycaemia. Current developments for early identification of hypoglycaemia risk combine improvements of available 'needle-type' enzymatic glucose sensors and noninvasive alternatives. Patient usability will be essential to demonstrate to allow their implementation for daily use in diabetes management.

KEYWORDS

algorithms, devices, diabetes mellitus, hypoglycaemia, sensors

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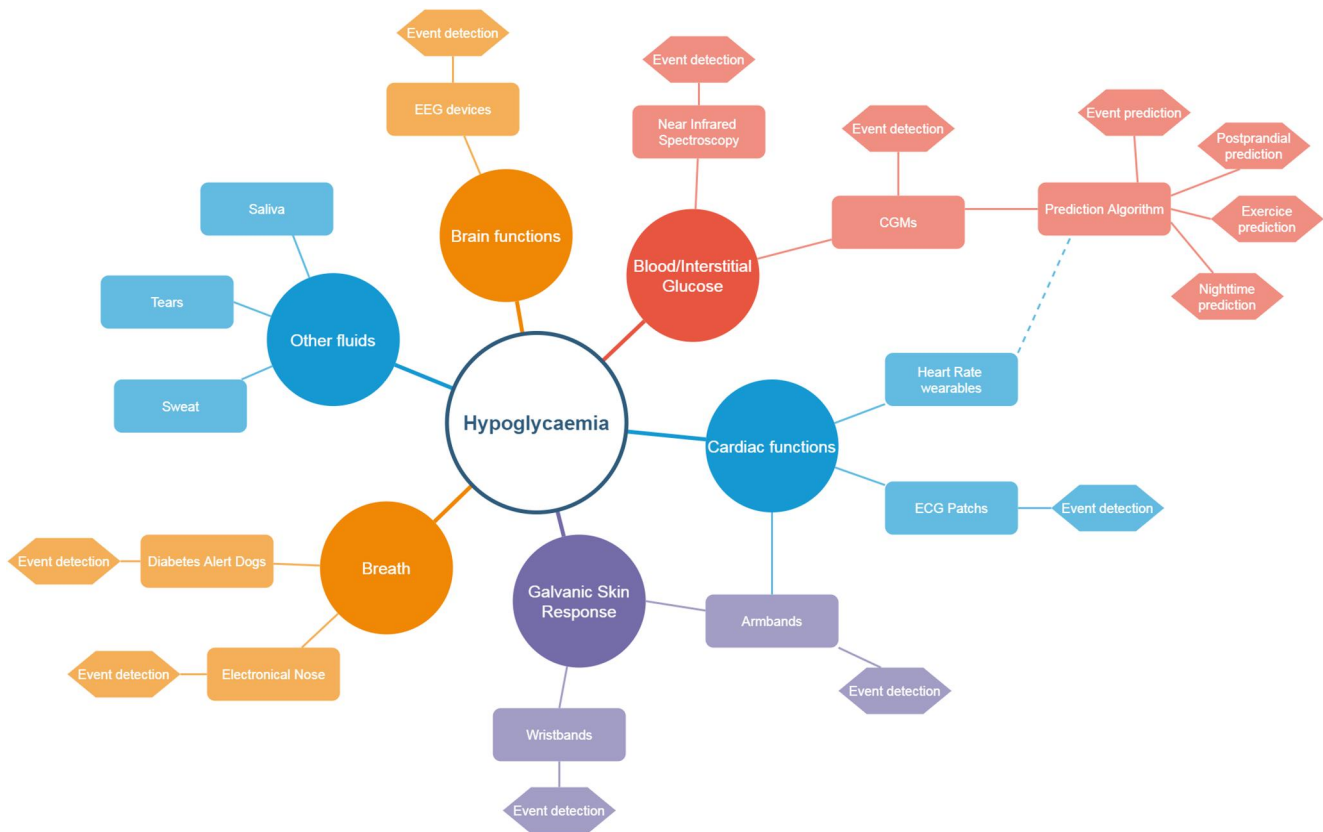


FIGURE 1 Mapping of hypoglycaemia detection and prediction techniques

1 | INTRODUCTION

Hypoglycaemia is one of the major threats for people with diabetes (PwD) in daily life, as it can result in symptoms that affect their mental agility and can lead to coma if not treated rapidly.¹ Psychological distress due to the fear of hypoglycaemia reduces the quality of life of PwD,² especially of persons with type 1 diabetes who have been reported as having twice higher occurrence of hypoglycaemia than those with type 2 diabetes.³

The fear of hypoglycaemia and associated symptoms lead many PwD to accept hyperglycaemic glucose values, as the easiest solution to avoid dealing with the management of unpleasant hypoglycaemic events.²

There are different definitions of hypoglycaemia based on the glucose levels, devices used and the impact of hypoglycaemia on the person with diabetes.^{1,4,5} Alongside these differences in glucose thresholds to define hypoglycaemia, there are huge inter—as well as intraindividual variations in the glucose levels at which hypoglycaemic events are experienced.⁶ For example, PwD with a long duration of diabetes and those with high glycaemic variability often have impaired awareness of hypoglycaemia and may not feel symptoms until glucose levels reach very low values, while those with sustained hyperglycaemia can feel symptoms of hypoglycaemia at much higher glucose values than the level of 3.9 mmol/L (70 mg/dl) defined in consensus documents.^{4,7}

In this paper, we provide an overview of new sensing technologies, other than electro-enzymatic and fluorescence-based ones present in currently marketed devices, which can be used to identify or prevent hypoglycaemia. Then, we address the algorithms being used or developed to enhance glucose monitoring and increase its accuracy, and to predict future glucose values, that can have a decisive role in predicting future hypoglycaemic events. Finally, we present hypoglycaemia detection techniques not based on glucose values but use one or different vital signs that are affected by low blood glucose values and hypoglycaemic symptoms. We finish with a discussion on the future of hypoglycaemia detection and prediction. The diversity of techniques presented in this review are represented in Figure 1 depending on the vital sign or fluid used for hypoglycaemia detection.

2 | METHODOLOGY

A literature review was performed using 'PUBMED', and 'IEEE' to find articles about technologies related to hypoglycaemia detection and prevention. After exploring and combining many search terms to ensure having the broadest results, we used the following terms: 'hypoglycaemia', 'blood glucose', 'glycaemia', 'prediction', 'predictive', 'detection', 'forecast', 'continuous glucose monitoring', 'CGM' and 'diabetes'.

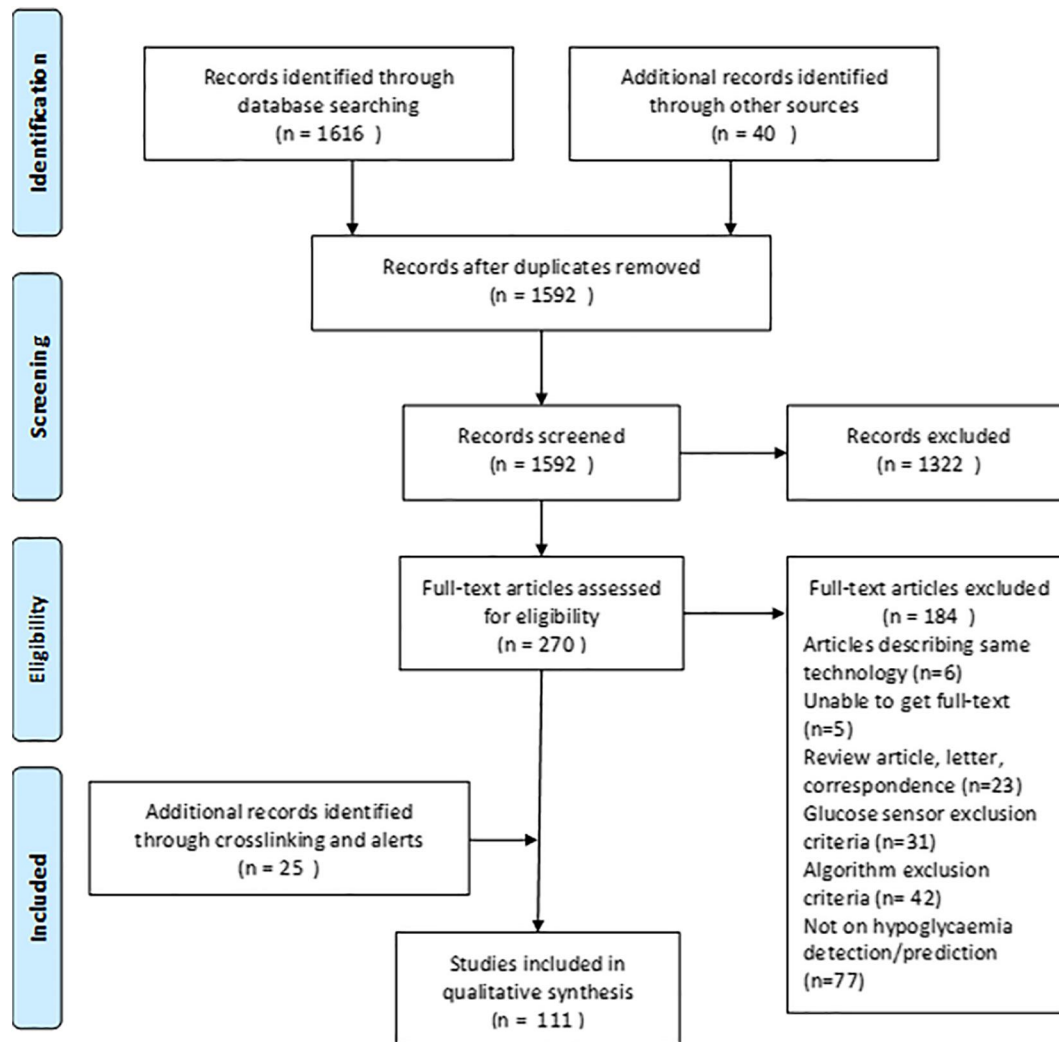


FIGURE 2 PRISMA flow diagram

The search was performed in January 2019 and was restricted to articles from 2013 onward, and gave in total 1616 results. M.C. and O.D. made a first selection of 270 articles. In parallel, an alert was set to avoid missing articles published after January 2019 dealing with these topics. References of selected articles were analysed to extract other related articles, and a complementary search in 'ScienceDirect' and 'Google Scholar' was used to find further information when necessary and to complete the review with original works on each subtopic identified. Monthly alerts and complimentary alerts helped to add 25 articles.

Only articles published after 2013 were retained for this review. New glucose sensors having a linear range detection wide enough for blood or interstitial measurement were eligible. For prediction algorithms, selected articles had to deal with glucose prediction and present details on the datasets used, methodology and performance metrics. We included algorithms that predicted glucose values in a defined prediction horizon, as well as those that specifically predicted hypoglycaemic events up to a maximum of 24 h in the future. Solutions and technologies for hypoglycaemia correction like new

glucagon formulations and closed-loop algorithms were excluded. Figure 2 presents the PRISMA flow diagram of this review.

3 | SENSING TECHNOLOGIES FOR BLOOD OR INTERSTITIAL GLUCOSE MEASUREMENT

The advent of enzymatic glucose sensors was a major revolution in the lives of PwD by allowing accurate self-monitoring of blood glucose (SMBG). However, SMBG allowed only intermittent measurement of blood glucose and PwD had to rely on their awareness of hypoglycaemia and appropriate timing of their daily tests to identify low glucose readings.

Continuous glucose monitoring (CGM) was an evolution that used the same principles of enzymatic glucose sensors, but through a new design of sensors allowed almost continuous (e.g., every 1–5 min) measurement of interstitial glucose (IG) for several consecutive days (e.g., 7–14 days). CGM empowered PwD to better manage their diabetes and minimise hypoglycaemia by allowing them

to see their glucose at any time, along with information about the rate and direction of change, and with many systems, providing alerts of impending hypoglycaemia allowing the PwD to take preventative action.

Both SMBG and CGM rely on an enzymatic reaction,⁸ mainly using glucose oxidase (GOx), but some systems can use glucose-1-dehydrogenase or hexokinase. After the first enzymatic reaction on glucose, subsequent reactions follow creating a current on an electrode. The measurement of the current allows calculation of glucose levels in the interstitial fluid by applying a calibration function. These electro-enzymatic reactions were chosen for their high-sensitivity (Se), the good linearity between the current and glucose level, and their range of detection going from 2 mmol/L (40 mg/dl) up to 40 mmol/L (400 mg/dl).⁹ However, at the extremities of the range of detection, these sensors suffer from a reduction of accuracy, with an increase in mean absolute relative difference (MARD) from an average of 9%–15% in most of currently available CGM systems¹⁰ to percentages over 20% for low glucose values.^{11,12} New advances in glucose sensor design may help to increase this accuracy at low glycaemia levels.

3.1 | Evolutions of enzymatic and electrochemical sensors towards a better accuracy

Over the last decades, development of nanomaterials opened a new path to improve sensors thanks to their size, morphology, and higher surface-to-volume ratios providing improved Se that could benefit glucose measurement. Although many publications report on sensors that are at experimental levels, and are sometimes far from having the range of detection needed for blood glucose monitoring, some articles presented sensors that may fit these needs.

Balakrishnan et al.¹³ propose a GOx surface modified with polysilicon nanogap, allowing a highly sensitive measurement with a limit of detection down to 0.6 $\mu\text{mol/L}$ (0.011 mg/dl) and a good linear range up to 50 mmol/L (900 mg/dl) fitting the criteria for blood and IG. Another proposed system works by immobilising GOx into an oxide copper and gold nanostructure,¹⁴ with a linear concentration range from 10 $\mu\text{mol/L}$ (0.18 mg/dl) to 20 mmol/L (360 mg/dl). Many other systems that are close to the requirements for clinical sensors are described, like CeO₂ nanorods,¹⁵ multiwalled carbon nanotubes ZnO nanoparticles,¹⁶ gold and ZnO nanorods¹⁷ combinations of enzyme models and graphene,^{18,19} all taking advantage of the nanostructures and materials to increase the Se of enzymatic sensors.^{20,21}

These nanomaterials are also proposed for nonenzymatic sensing, using platinum, gold, nickel, copper, palladium and other composites,^{22,23} but only a few show a linear range inside the physiological levels of blood or IG in PwD. From this small number, we have a CuO NPs Ag electrode with a range from 0.05 to 18.45 mmol/L (0.9–332 mg/dl),²⁴ a Pd–Pt graphene electrode,²⁵ a Ni(OH)₂ nanostructure with a glucose range detection of 0.01–30 mmol/L,²⁶ a Pd NPs silver electrode.²⁷

However, the path to market of these newly designed sensors is long and many steps are still needed. After initial laboratory accuracy assessments, reproducibility, biocompatibility and other fluid components' interferences must be evaluated. Toxicity evaluation is also necessary for these materials that may be present in invasive devices to ensure safety of use. They must also fit to industrialisation processes and storage requirements, and be amenable to scaling and quality control. Only after succeeding in these step will real world data collection from clinical studies be possible, that would allow us to know the true level of improvement of accuracy and MARD reduction of these next-generation sensors.

3.2 | Noninvasive blood glucose sensors

Noninvasive methods for CGM could change the life of PwD suffering from frequently occurring and severe hypoglycaemia.

Currently available noninvasive technologies do not reach the same accuracy as electrochemical minimally invasive sensors present nowadays in CGM.^{28,29} It remains uncertain whether they will reach standards like ISO-15197 or UCM 380327 for medical device approval that would make them suitable for closed-loop systems and automated advisory systems. However, these devices could allow better acceptance by the patients due to their noninvasiveness, as well as more affordable access to CGM for many patients thanks to reduced need for expensive consumables.

Amongst the noninvasive continuous monitoring solutions we identified in development, many use optical technologies. For example, 'Wear 2b[®]' from Israel³⁰ and 'Prediktor Medical[®]' company from Norway³¹ are developing devices with near-infrared (NIR) spectroscopy, while 'D-pocket[®]' and 'D-band[®]' devices (Dia-MonTech)³² are using mid-infrared spectroscopy and photothermal detection.

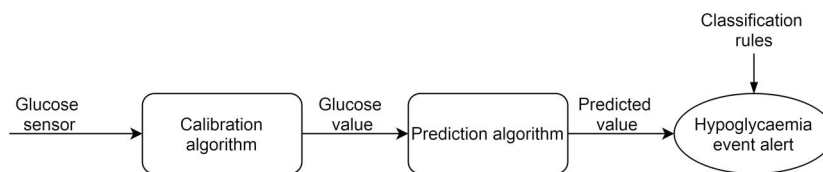
Other minimally invasive approaches need also to be mentioned, like 'K'Watch[®]' device (PkVitality, France)³³ using micro-needles to measure IG at skin surface and 'SugarBeat[®]' device (Nemaura Medical)³⁴ that uses reverse iontophoresis to extract interstitial fluid through two electrodes. These two devices are near-to-market and report MARDs almost similar to commercially available enzymatic CGM systems, despite using minimally invasive methods to access the interstitial fluid.

For a better insight in non-invasive techniques, we recommend recent reviews by Avari et al.²⁸ and Gonzales et al.²⁹

4 | ALGORITHMS FOR GLUCOSE AND HYPOGLYCAEMIA PREDICTION

In commercially available CGM devices that use an enzymatic sensor, algorithms are needed to convert measured electrical current into a glucose value, and in some cases to correlate the IG value to the blood glucose (BG) value that may have a different linear range, and also to reduce the delay of 10–15 min^{35–37} between tissue and blood.

FIGURE 3 Process from glucose sensing to hypoglycaemic event alert found in many available devices



By consequence, the first steps to better detect hypoglycaemia are to improve the calibration algorithms that must be performed to calculate real blood glucose value allowing faster and more accurate detection of a low values.

4.1 | Calibration algorithms

Early CGM systems used first-order linear functions or Kalman filters as calibration algorithms,^{38,39} with one or two SMBG entries per day. Recent developments in calibration algorithms pave the way to a reduction of capillary calibration needs and an improvement in MARD.

An algorithm presented by Mahmoudi et al.⁴⁰ was used to reduce requirement for calibration.⁴¹ It uses three steps, starting by a rate-limit filtering to ensure physiological limits of rate of change are not exceeded, then a selective smoothing to reduce the noise of the signal, followed by a regression that calculates the corresponding glucose value using the electrical signal and the SMBG entries. This algorithm demonstrated better accuracy in the range of low blood glucose levels.^{41,42}

Some other groups⁴³⁻⁴⁵ used a regularised deconvolution to compensate for the difference between blood and IG, followed by linear regression using two SMBG calibration values. The algorithm was then further developed to use less calibrations using a Bayesian framework that reevaluates calibration parameters at each iteration to a final version using no calibration,⁴⁶ making the simple first-order linear functions more accurate by taking into account the whole 7-day period and obtaining a reduction in MARD of 1.2%.

Other teams have tried to use past weeks' data of previous sensors, refining the calibration parameters for each new sensor insertion.^{47,48} These algorithms cannot be easily used in real-time in wearable devices, but the increasing usage of smartphones for glycaemic monitoring may open the way to such implementations.

These attempts show that using more complex techniques can help to reduce the MARD by more than 1%, and may improve performance in the hypoglycaemic range where CGM systems are currently less accurate.^{12,42,46}

4.2 | Prediction algorithms

After improving the accuracy of CGM devices, through new sensors and more complex calibration algorithms as presented earlier, another step towards further improving the quality of life of PwD and their ability to counter hypoglycaemia are predictive algorithms and

alarms as presented in Figure 3. They allow the patients to act early and effectively prevent episodes of hypoglycaemia.

Similar to calibration algorithms, first-generation of prediction algorithms used linear regressions or Kalman filters,³⁹ which are simple calculation techniques that can be embedded in monitoring devices and use past data to allow a short-term prediction (20-min prediction horizon for hypoglycaemia or hyperglycaemia alarm in current commercial devices).

While many articles present different prediction algorithms, only a few tried to assess their clinical efficacy and benefits in real life or at least in simulations.

A first in silico study led by Zecchin et al.⁴⁹ with 50 virtual patients from the UVA/PADOVA simulator compared the duration of hypoglycaemic events in three scenarios: one when hypoglycaemia was not detected by any device, one where the patient took rescue carbs when crossing hypoglycaemia threshold, and one when 30-min predictions alerted about hypoglycaemia. The simulation results show that hypoglycaemia alert reduced time spent in hypoglycaemia from 17.7% to 4.7% in the scenario with threshold alert and to 1.2% in the scenario with predictive alert.

These predictions help patients to take clinical decisions in their treatment, as shown in an early study.⁵⁰ Twelve patients were asked to record their decision making around hypoglycaemia, comparing their usual care with a system that informed them of a 30-min prediction. Twenty percent of the patient's decisions were changed and led to improved glycaemia. However, in some cases overtreatment led to hyperglycaemia.

An observational study⁵¹ showed that the activation of such predictive hypoglycaemia alarms reduced time below 3 mmol/L (54 mg/dl) by almost 40%. Another retrospective study⁵² found that predictive alarms prevented 59% of low glycaemic values.

Incoming years, we expect an increase of clinical evaluations of such algorithms, with the integration of prediction techniques in CGM systems and other devices, even though from a logical perspective the benefits for patients seem obvious through their empowerment to take proactive decisions before reaching critical glucose levels. However, education as for every new device will be necessary to prevent the counter effects of over reactions.

4.3 | A diversity of modelling strategies

Numerous factors can affect blood glucose levels and induce hypoglycaemic events such as insulin dosage, meal consumption, physical activity, sleep quality, alcohol consumption, interfering medication, stress and emotions, leading to a diversity of features that can be

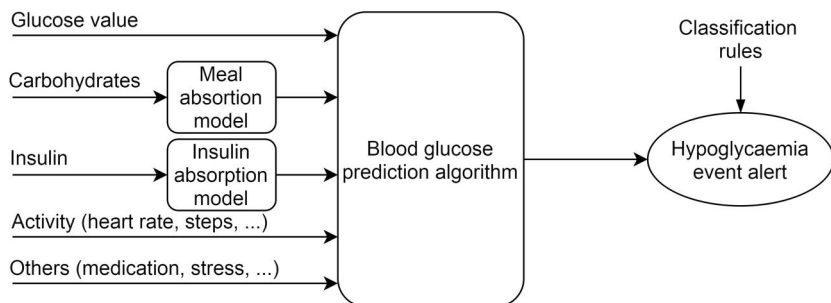


FIGURE 4 Multivariable blood glucose prediction. In addition to glucose value, others inputs are added to increase accuracy. A blood glucose prediction value is calculated, and classification rules allow evaluating the incoming hypoglycaemia event

used in addition to blood glucose history to develop predictive algorithms. The increasing availability of devices like CGM systems, insulin pumps or connected insulin pens, meal-recognition apps, physical activity wearables and the increasing usage of CHO counting amongst PwD allow collection of a variety of nonglucose data that can be employed to predict blood glucose.

We found 48 relevant publications^{53–100} that presented a prediction algorithm published between 2013 and 2020 showing the recent increasing interest for this topic. Information on these algorithms is presented in appendices.

4.4 | Prediction inputs

In these publications, a diversity of strategies was used depending on the data collected and their complexity and the algorithm objective. More than half of the algorithms used one or two additional data inputs, usually insulin doses or carbohydrates (CHO) or both. These two inputs are easily accessible as they are almost always collected in bolus advisors used in sensor augmented pump trials with enough accuracy for modelling purposes. For a better interpretation by prediction algorithms, these two additional inputs are processed in almost one third of reviewed articles by physiological models to extract additional features describing the absorption dynamics of insulin action^{101–104} or meals.^{104–107}

The addition of insulin and CHO data to CGM in prediction models can slightly improve the performance of algorithms. However, outside of clinical studies where patients are specifically selected for their ability to carb count, using the CHO input in real life setting seems difficult to achieve. To avoid this burdensome task for patients, three publications^{70,92,95} proposed to use meal timestamps to inform the prediction algorithm of this event. Another research team⁵⁸ proposed that meal entries could be simplified by classifying them with a five-level scale from very light to very heavy meal.

Physical activity is the other major input impacting blood glucose level. Nine studies investigated the use of armbands or wristbands to collect information on heart rate,^{71,93,94} energy expenditure^{75,76,85,99,100} or the number of steps,⁸⁷ to augment the predictability by this input. In all cases where comparisons have been made, the addition of a signal informing the algorithm about activity increased its prediction performance, even for commercial devices. This shows that in real-life setting, many accessible devices are

accurate enough for this purpose. The difficulty will be more on the technical side to integrate different models and take into account the diversity of data structure for each device. Finally, stress,⁸⁴ medication,⁷⁰ daily events and circadian rhythms⁸⁶ were also investigated as potential inputs, and could be helpful to differentiate prediction models for daytime and night-time.

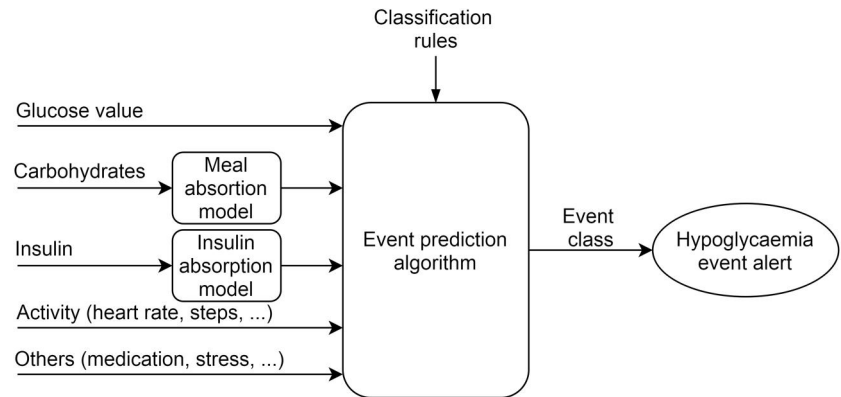
4.5 | Prediction algorithms and outputs

After this step of input selection, and the use or non-use of meal and insulin physiological models, an algorithm is selected depending on the purpose of the algorithm and its ability to process different type of inputs. For blood glucose prediction, where the output is a value a few steps ahead, the algorithms used are regressive models (ARM, ARMAX, ARIMAX ...), different types of neural networks (ANN, CNN, RNN, ELM, ESN ...), genetic algorithms and grammatical evolution, support vector machines (SVMs) and support vector regressions, Gaussian processes, self-organising maps (SOM) and kernel ridge regression. In some cases as illustrated in Figure 4, the authors added a final step with rules to create a hypoglycaemia or hyperglycaemia warning using computed blood glucose values from the prediction algorithms.

Another strategy presented in Figure 5 is to predict directly the occurrence of a hypoglycaemic event in a defined prediction horizon, without computing blood glucose values. This strategy is mostly used for postprandial hypoglycaemia, exercise-induced hypoglycaemia and night-time hypoglycaemia, where the aim is to inform the PwD quite early, at meal time or bedtime or prior to the start of exercise to reduce the risk of having such adverse event in the following hours. The algorithms used are mainly classification algorithms like SVM, SOM, classification trees, linear discriminant functions, random forests and also ANN and grammatical evolution.

Finally, some teams^{53,59,62,71,73,78,81,83} merged different algorithms having the same output to increase the models' performance, taking advantage of each algorithms characteristics. Vehi et al.⁸⁷ took this strategy one step further, by proposing three algorithms for each situation, one predicting hypoglycaemia in the next hour using grammatical evolution, which can be enhanced by another algorithm for postprandial hypoglycaemia risk in the next 4 h following the meal using SVM, and another algorithm trained for night-time hypoglycaemia using ANN.

FIGURE 5 Multivariable event prediction. In this other model, the algorithm is trained directly for hypoglycaemia event prediction



The diversity of approaches, inputs used, algorithms and the number of publications in the last few years, shows that this field of research is expanding and researchers are still exploring all the capabilities that machine learning and artificial intelligence offer. New algorithms are created every year,¹⁰⁸ and are tested rapidly by different teams on different blood glucose datasets.

Most studies were performed in people with type 1 diabetes (T1D) who are most in need of this type of algorithm and are more challenging for algorithms due to their high glucose variability and Se to external factors than people with T2D. We can also highlight that in the last two years, many publications used large datasets of more than 80 patients with collection duration of several weeks or months. This shows an increasing availability of qualitative datasets collected during clinical studies that can be exploited for machine learning purpose.

4.6 | Performance metrics

The performance metrics are key elements that allow determination of the accuracy of the developed model and its ability to predict correctly blood glucose or an adverse event. Some commonly used metrics are purely mathematical and give an insight on the level of errors made by the presented model. The most used mathematical metric is root mean square error (RMSE), followed by mean absolute error (MAE), mean absolute difference (MAD), MARD, energy of the second-order difference (ESOD), relative absolute difference (RAD) and sum of squares of the glucose prediction error (SSGPE). RMSE, MAE, MAD and SSGPE represent the errors between predicted and real values, while MARD and RAD are more sensitive to errors in low glucose values. ESOD is an indicator of the variability and the oscillations present in the predicted glucose profile, the lower the value the smoother is the profile.

For better clarity, some authors also use clinical evaluation metrics that can reflect the impact of prediction on clinical decisions and some were developed specifically for diabetes-related technologies. Metrics like time lag or time gain¹⁰⁹ give an insight of the average time gained by patient before his real glucose level reaches the predicted value, and represent the true prediction horizon.

'J Index'¹⁰⁹ was developed specifically for blood glucose prediction algorithms, and combines ESOD and time gain to reflect the clinical usefulness of the predicted value.

Error grids were developed to assess the clinical accuracy of SMBG, classifying the error between the assessed device and a standard reference measured by laboratory test in different zones, each one corresponding to a level of clinical risk in case of difference between the real and the measured value. Many teams used the classical Clarke's error grid¹¹⁰ and Parkes Error grids¹¹¹ that were intended for assessing the accuracy of SMBG. A few teams used the continuous glucose-error grid analysis (CG-EGA)¹¹² designed for assessing the accuracy of CGM, and one team used prediction (PRED)-EGA.¹¹³ This last error grid was developed specifically to assess the clinical accuracy of prediction algorithms, modifying the way rate of change is evaluated in CG-EGA which results in a reduction of misclassified cases.

The accuracy of hypoglycaemia event prediction uses more standard metrics like receiver operating characteristics curves, Se, Sp, positive predictive value, false alarm rate, accuracy, Matthews correlation coefficient and F1-score. However, we see in some publications differences in the way hypoglycaemic events are defined. Some authors considered the hypoglycaemic event as crossing the BG value of 3.9 mmol/L (70 mg/dl), others as having two or three BG values of 3.9 mmol/L, and others used also the second level of 3 (54 mg/dl) or 2.8 mmol/L (50 mg/dl).

This variety of performance metrics makes it difficult for an external reader to compare results from different publications. We also regret the lack of use of clinical performance metrics, especially the ones like J-Index and PRED-EGA or CG-EGA and time gain that could be more pertinent to validate the accuracy of the presented algorithms.

5 | NONGLYCAEMIA-BASED DETECTION TECHNIQUES

Another axis of research in the last years was the development of technologies for hypoglycaemia detection using other sources than blood or IG, exploring other metabolic alterations that can occur during a hypoglycaemic event.

5.1 | Electrocardiogram-based hypoglycaemia detection

The impact of low blood glucose levels on the electrical activity of the heart has been studied in the last years.¹¹⁴⁻¹¹⁸ Reports show a prolongation of the QT interval, an increase in heart rate variability (HRV), and changes in cardiac repolarisation during hypoglycaemic episodes. Thus, using electrocardiogram (ECG) changes could be a noninvasive way to detect the onset of hypoglycaemia.

The development in the last decade of new ECG wearables enabled easy collection of cardiac signals and opened the way to ECG-based hypoglycaemia detection through deep learning algorithms.

First attempts to predict hypoglycaemia from ECG were made by the Nguyen HT team in many publications,¹¹⁹⁻¹²⁶ using the same dataset of 15 T1D children overnight, with an ECG Holter and CGM measurement. Many algorithms were used in these publications like neural networks or extreme learning machines, and inputs were QTc and HRV, with a learning approach that did not take into account interindividual variations. The best results obtained a Se of 80% and a Sp of 50% for only night-time hypoglycaemia.

A publication in 2016¹²⁷ using data from an ECG Holter from outpatients over two days showed that significant prolongations of QT intervals can occur and be detected during daytime in real-life setting.

Another proof of principle study published in 2019¹²⁸ used a wearable device in 23 T1D outpatients, the 'VitalPatch[®]' (Vital-Connect) that can be placed on the chest for 5 days and can measure heart rate. Results showed that 55% of day and night hypoglycaemias were clearly detectable using only HRV, and 27% showed an atypical pattern.

These two studies showed that theoretically, QTc and HRV could be two ECG features that can be used for noninvasive hypoglycaemia detection, whether patients do or do not have diabetes, and that having cardiovascular autonomic neuropathy does not influence their ability to detect these measurable changes during hypoglycaemia.¹²⁹ This last characteristic will have to be further confirmed in patients with long-standing diabetes or those with confirmed cardiac autonomic neuropathy.¹³⁰

While working on this review, an original work was published that leverages these approaches of hypoglycaemia detection through ECG to a next level, using a deep learning algorithm to detect the beginning of the event using the raw ECG signal directly without feature extraction.¹³¹ After collecting and processing data from eight healthy patients using a wearable ECG patch that records ECG signal and actigraphy, two different algorithms were used to detect night-time hypoglycaemia. They obtained good results with a Se, a Sp and an accuracy around 84% respectively for both models. The originality of this work, beside using real-life raw data from commercialised ECG wearables, is using a person-specific approach with a learning process for each individual patient. This allows the system to account for individual differences between subjects as visible in Figure 6, while all other studies were cohort-based approaches.

These different studies show that ECG could be used in real-life conditions for helping patients to detect hypoglycaemic events. Improved devices and algorithms can make these algorithms more accurate and easier to implement in real-life, which paves the way for new tools. If T1D patients may not be the first beneficiary of these technologies, ECG-based algorithms could be useful for patients without diabetes suffering from night-time hypoglycaemia, due to other conditions such as insulinoma, nesidioblastosis, endocrine, kidney, liver or heart disorders, anorexia, tumours.

5.2 | Electroencephalogram detection

One of the other symptoms of hypoglycaemia is a decrease in cognitive function. Hence, time series electro-encephalogram (EEG) can also be a good candidate for severe hypoglycaemia event detection (below 2.2 mmol/L), as it was confirmed by the first studies where EEG and blood glucose were recorded simultaneously.¹³²⁻¹³⁴ Figure 7 presents an illustration of these difference of EEG signal during hypoglycaemia.

In recent years, in addition to their ECG studies, Nguyen and his team^{135,136} have also conducted several studies with EEG. In their first attempts, they collected overnight EEG and BG data every 5 min through 'YSI glucose analyser[®]' (YSI Life Sciences) from five T1D adolescents, and performed insulin-induced hypoglycaemia. Significant changes in EEG alpha band were observed during hypoglycaemia, and achieved detection performance results of 75% Se and 60% Sp. Further studies with three more volunteers and using other algorithms slightly improved their results¹³⁷⁻¹³⁹

A Danish team in association with the company 'UnEEG medical[®]' (Denmark) have developed a wearable EEG for ambulatory and studied hypoglycaemia detection. In their first studies before 2013 where they investigated insulin-induced hypoglycaemia, they concluded that EEG changes during low blood glucose events were detectable during both day- and night-time.^{140,141} This work was followed by another publication in 2016 where the same experiment was performed in eight prepubertal children with T1D in three phases to record EEG during daytime hypoglycaemia and during sleep.¹⁴² The same algorithm developed for adults detected all hypoglycaemic events during daytime, but had too many false alarms during sleep, indicating that it needed a specific adjustment for children during night-time. A later study¹⁴³ was performed with 24 T1D adults who underwent two hyperinsulinemic hypoglycaemic clamps on two subsequent days, to assess if brain changes were different after antecedent hypoglycaemia, and found no significant differences in EEG records. The conclusion was that EEG-based detection can be used as hypoglycaemia alarm in daily use without suffering from loss of accuracy through successive episodes. On average, during these studies, EEG was able to detect a blood glucose level around 2.2 mmol/L (40 mg/dl), and between 15 and 20 min before reaching the nadir point, giving just enough time to prevent a severe hypoglycaemic episode.

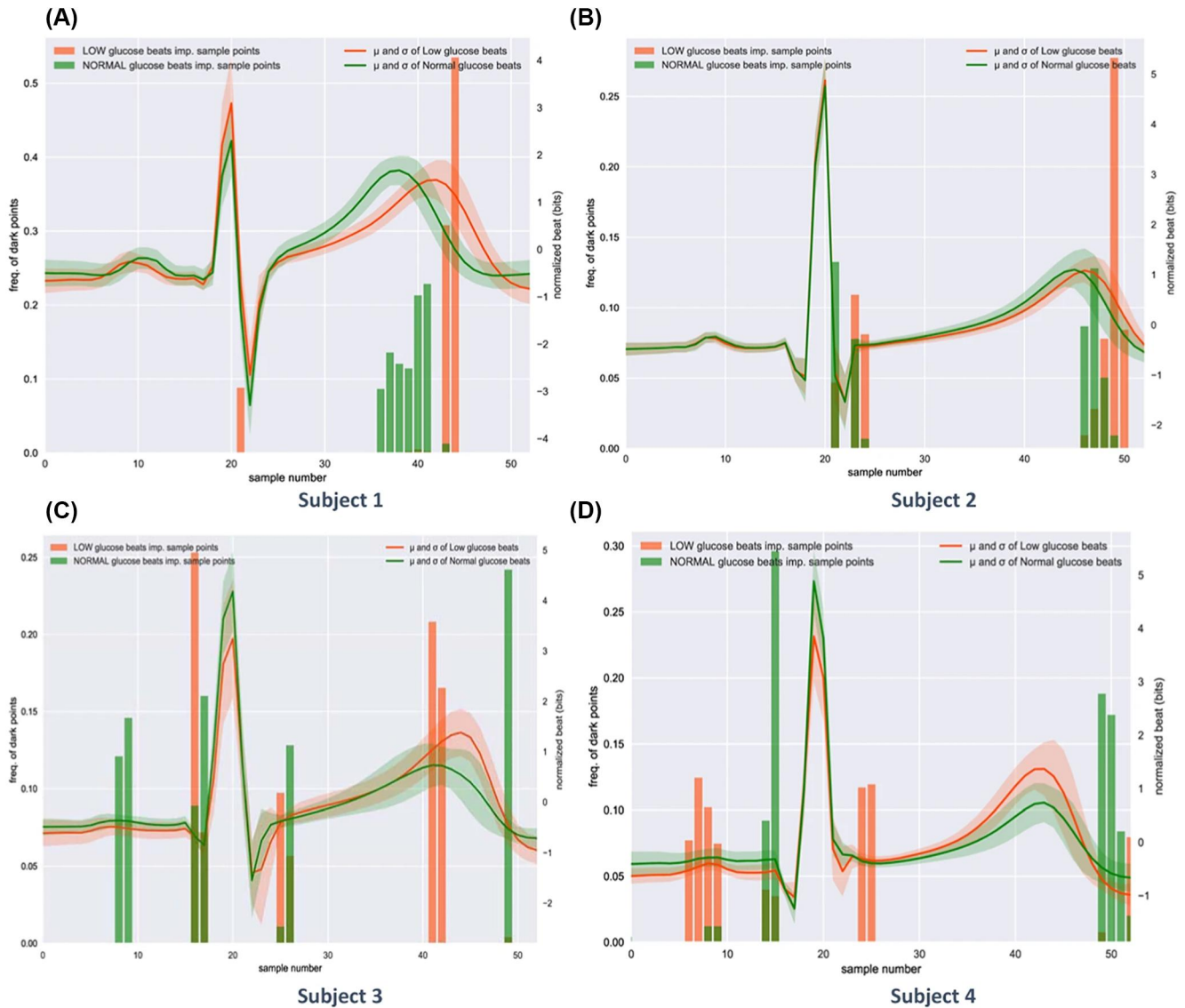


FIGURE 6 Illustration of interindividual differences in heartbeats during hypoglycaemia events. The solidlines represent the mean of all the heartbeats that correspond to each subject in the training dataset: green during normal glucose levels, red during hypoglycaemic events. The comparison among four different subjects highlighted the fact that each subject may have a different ECG waveform during hypoglycaemic events. For instance, Subjects 1 and 2 present a visibly longer QT interval during hypoglycaemic events, differently from Subjects 3 and 4. Reproduced from Porumb et al.¹²⁹

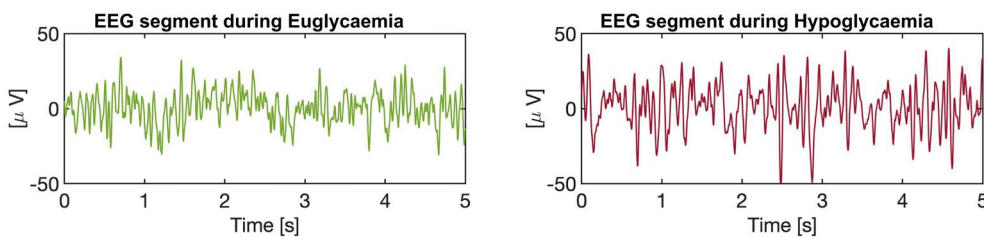


FIGURE 7 Encephalogram (EEG) segments during euglycaemia and hypoglycaemia. Each segment represents a 5-s interval of EEG recordings during each phase, showing a higher amplitude in the low-frequency bands and greater regularity during hypoglycaemia episodes

After this series of clinically controlled trials, an ambulatory 3-month study¹⁴⁴ was performed with eight T1D persons to evaluate the efficacy of an EEG alarm device in real-life conditions. CGM was

recorded for two periods of 5 days and SMBG was performed at each EEG alarm. One person withdrew from the study due to device discomfort, and 659 days were recorded. Sixteen alarms were

triggered by the device at a median value of 2.4 mmol/L (43 mg/dl), and all subjects were able to take preventive actions before progression to severe hypoglycaemia. No false negative alarms were reported for hypoglycaemic events needing external help, but patients experienced 2.9 false alarms/week during daytime (and only 0.2/week during night-time).

In all these studies, the '24/7 EEG SubQ[®]' (unEEG medical) was used, a device in which a small part is implanted behind the ear, and an external device powers the implanted part, processes the signal in real-time and launches the alarm if an event is detected.

New marketed devices opened the way for continuous real-life measurement of ECG and EEG signals with enough accuracy to allow the development of algorithms for severe hypoglycaemia detection. These devices are not intended to enter in competition with CGM systems, but can be an alternative for some patients prone to hypoglycaemia. However, ECG seems more suitable for a daily use, being noninvasive and easier to wear and hide.

5.3 | Other hypoglycaemia detection techniques or indirect blood glucose estimation

Beside EEG and ECG, other physiological signals that can be altered during a hypoglycaemic event have also been investigated.

Galvanic skin response (GSR) was studied extensively to develop alarms for night-time hypoglycaemia since the 80s, taking into account alterations in skin temperature, perspiration and electrodermal activity at event onset. Two commercial devices were produced and tested in the 80s, 'Diabalert[®]' and 'Sleep Sentry[®]', but clinical studies showed a low accuracy and many false alarms.^{145,146}

Another available device on the market is 'Diabetes Sentry[®]' (Diabetes Sentry),¹⁴⁷ a wristband that measures the GSR and alerts patients in case of hypoglycaemia. The website states a rate of 90% alarm success, but no publication on this device was found to confirm these claims.

The 'SenseWear Pro Armband[®]' (Bodymedia) is a noninvasive multisensor that measures GSR, but also skin temperature, ECG and body motion. This device as mentioned previously has been used with CGM to increase prediction accuracy,⁷⁵⁻⁸⁴ but it was also evaluated for glucose estimation. In a publication by Sobel et al.¹⁴⁸ the device was evaluated in 41 T1D and T2D patients. They underwent two tests to assess its accuracy in evaluating blood glucose level in dynamic conditions, during a glucose increase using an oral glucose tolerance test and during a glucose decrease during a treadmill test. During the study, reference blood glucose was measured every 5 min using an intravenous catheter, and a CGM was used for model training and for comparison. During the meal test, the device MARD was 26% versus 18% for the CGM, and for the exercise test the device MARD was 16% versus 12% for the CGM; and 95% of the readings were in Zone A + B in the CEG. However, both device and CGM were less accurate for low-blood glucose readings, with only 20% hypoglycaemic values correctly estimated by the armband and 8.9% by the CGM.

This study, while confirming the limitations of CGM for the accurate measurement of high and low values and during rapid glucose variations, shows that this device measuring four separate physiological signals simultaneously can be almost as accurate as CGM. Nevertheless, these results need confirmation in larger trials and under real-life conditions, to avoid the risks of overfitting of the learning algorithm than can occur in small datasets.

Other teams tried to detect blood glucose levels or hypoglycaemic events through volatile organic compounds (VOCs) present in breath, mainly acetone, methyl nitrate, ethanol, methanol¹⁴⁹⁻¹⁵¹ and isoprene,¹⁵² that change with glucose variations. Shrestha et al.¹⁵³ collected breath samples from 52 PwD and analysed their composition, then trained a linear discriminant analysis to detect breath samples in hypoglycaemia and found seven main VOC that are significantly related to hypoglycaemic state. They succeeded in a classification of breath samples with a Se of 91% and Sp of 84%. In two other studies, an experimental device was presented and tested with artificial samples simulating VOC concentrations in real breath samples at different levels of blood glucose, and with different levels of acetone and ethanol. They obtained an accuracy of 97% for hypoglycaemia breath samples in their tests¹⁵⁴ and developed a prototype with the shape of a wristband.¹⁵⁵

Tronstad et al.¹⁵⁶ presented another prototype with 'Prediktor Medical[®]' from Norway, combining skin temperature, bioimpedance and NIR spectroscopy to predict glucose trends during hypoglycaemia. Their prototype was not reliable enough for low blood glucose threshold detection, and they concluded that a combination of other sensors with NIR could allow a noninvasive detection. Another publication by the same team¹⁵⁷ combined a sudomotor activity sensor, ECG (heart rate and QTc), NIR and bioimpedance spectroscopy. In this second publication, the aim was to detect hypoglycaemia using this combination of vital signs that are altered during low blood glucose events, and for classification purpose the threshold was defined at 4 mmol/L (72 mg/dl). The investigators succeeded in detecting almost all events with a Se of 95% and a Sp of 93%. In both trials, 20 T1D patients with impaired hypoglycaemia awareness were recruited, and data were collected during hypoglycaemic and euglycemic clamp studies.

Karunathilaka et al.¹⁵⁸ used also NIR spectroscopy to generate a noninvasive hypoglycaemia alarm, that was tested using an experimental setting that mimics glucose excursions in the human body, with an aqueous layer containing different levels of glucose and urea that can dynamically vary thanks to a pump and a tissue phantom composed of collagen and keratin to simulate human skin. This complex experimental setting allowed them to approach real life settings with blood glucose variations and different skin thicknesses and tissue orientations. They succeeded with this noninvasive technique with only 3.3% of false alarms in the first experimental procedure and a correct classification up to 93% in the second and more complex experimental procedure. Further testing with animal models is expected to complement these first results.

TABLE 1 Summary of main technologies for hypoglycaemia detection and prediction

	Next-gen sensors	Prediction algorithms	EKG detection	EEG detection	NIR detection	Breath detection	Galvanic skin response detection
Prevention level	-Detection at low threshold	-Prediction before reaching low threshold	-Detection at first symptoms -Severe hypoprevention	-Detection at first symptoms -Severe hypoprevention	-Detection at low threshold and at first symptoms	-Point of care test -Severe hypoprevention	-Detection at first symptoms -Severe hypoprevention
Level of development	-In silico trials -Experimental sensors	-In silico trials for complex models -First algorithms available	-Small cohort trials -Existing wearable prototypes	-Small cohort trials -Existing wearable prototype	-In silico trials -Experimental prototypes	-In silico trials -Small cohort trials -Experimental prototype	-Commercial devices existing
Remaining gaps	-Toxicity and biocompatibility trials -Industrialisation process	-Real-life validation for multivariable algorithms	-Validation in patients with heart diseases and in large trials	-Validation in large trials for day and night	-Development of wearable NIR devices	-Development of a prototype for continuous use -Postmeal validation accuracy	-Accuracy improvements
PROs	-Better sensibility and accuracy -MARD reduction -Possible reduction of invasiveness	-Mid-term and long-term prediction -Possibility to combine with closed-loops	-Noninvasive measurement -Good accuracy	-Good night-time accuracy	-Noninvasive measurement -Possibility to improve towards CGM	-Noninvasive measurement	-Noninvasive measurement
CONS	-Invasive and expensive devices	-Risks of patients' overreactions -Need to inform algorithm with data	-Device lifetime of few days	-Invasive device	-Unknown CONS (early stage of development)	-Needs to breath towards the device in actual prototypes	-Low accuracy in patients with hypo unawareness

Abbreviations: CGM, continuous glucose monitoring; CON; MARD, mean absolute relative difference; NIR, near-infrared; PRO.

Even though we cannot categorise them as a technology or device, diabetes alert dogs were evaluated in some publications.^{159–161} If investigational studies using perspiration samples show accuracy up to 90% for hypoglycaemia detection, real-life studies show poorer efficacy. Two studies^{159,160} with respectively 8 and 14 patients and their dogs using blinded CGM systems show a Se around 30% with a large variability between dogs (from 0% to 100%). Despite this lack in accuracy, these dogs help patients and their relatives in improving their quality of life and their confidence in managing their diabetes.¹⁶¹

Some other fluids have been investigated for glucose monitoring, like tears, sweat, urine and saliva as their glucose concentrations seem to correlate with blood glucose concentrations, but due to higher lag-times between these fluids and blood, they cannot be used for efficient hypoglycaemia detection or diabetes management.

The alternative techniques presented in this last chapter and resumed in appendix files used very different strategies, some being more realistic for ambulatory use than others. However, we must not forget that for an adoption by final users under real-life conditions, such devices must achieve good accuracy, a continuous measure of vital signs to allow a real onset detection and not only point-of-care testing, and present a low burden for patients and affordable costs for payers.

6 | DISCUSSION

In this review, we present many technologies for hypoglycaemia detection and prediction, with different levels of complexity and advancement that are summarised in Table 1.

Without any doubt, CGM will remain the first and main tool for hypoglycaemia detection. New enhancements in nanomaterials along with more complex and effective calibration algorithms will help the next generation of CGM systems to improve their accuracy, especially at low glucose levels.

Moreover, prediction algorithms provide a promising solution for PwD. Some algorithms are already implemented in commercial devices such as 'G6C' device (Dexcom)⁵¹ and 'Guardian Connect©' (Medtronic)⁵² and can reduce hypoglycaemic events by more than half. Connectivity of CGM systems, insulin pumps and activity wearables with smartphones gives the capacity to use multivariate algorithms and permits cloud-based complex calculations. One of the major shared points between many reviewed prediction algorithms is that adding CHO intake, insulin doses or activity measurements helps increase the accuracy over a mid-term or long-term prediction horizon. Besides, combining different models may permit several levels of hypoglycaemia alarms, each one trained for a specific situation like meals, exercise or night-time.

Unfortunately, we observed that most algorithms have been trained on small datasets or on clinically obtained datasets from highly motivated patients, which are far from real-life settings where patients often do not routinely record events like CHO or exercise needed to inform these algorithms. Access of research teams to big

datasets is needed for increasing the performance of these algorithms.

We can expect also the integration of these complex and multivariate algorithms in hybrid-closed loop systems that are now entering the market.

Clinical assessment of the safety and efficacy of prediction algorithms is still in its infancy, with only a small number of papers in the last 2 years. Hence, it will be necessary to develop specific protocols to collect data on how patients use them in real-life settings; so that clinical guidelines can be written and patients informed to avoid misuse and overreactions, as was observed in one publication.⁵⁰

People with T1D who require permanent monitoring of glucose levels are not the only ones exposed to hypoglycaemia. Other pathologies and some treatments can also induce hypoglycaemia. Alternative methods to CGM systems and CGM-based prediction algorithms can be useful for patients who do not need an expensive system for real-time and continuous glucose measurement.

GSR is already used in some marketed devices, and is still being investigated in other prototypes. Its combination with heart rate and other vital signs allows blood glucose estimation, albeit with a combined CGM-use for the training phase. This technology that was explored since the eighties suffered from poor accuracy in early commercialised devices, but is still improving. It may become a good alternative to CGM systems for noninvasive hypoglycaemia detection.

One of the most promising methods, that seems near-to-market, is ECG-based detection of hypoglycaemia. The most recent studies were performed with wearable noninvasive patches allowing real-time ECG capture, and algorithms were tested in real-life, during day- and night-time, and showed good accuracy in hypoglycaemia detection. Some such devices are already on the market and are used for patients with heart diseases. Thus, we can expect companies that developed these devices may be able in the next years to add some extra features such as hypoglycaemia detection. But we need to point out that these devices only have a short duration of use, and consumable costs could make them expensive for long-term continuous monitoring. Current smartwatches do not permit continuous ECG monitoring and need a manual input to start ECG measurement for a few seconds. The evolution of these smartwatches towards continuous monitoring would increase the acceptability of ECG-based hypoglycaemia detection for patients.

The situation is the same for EEG detection technique with a similar level of advancement. However, current EEG-based devices are more invasive than ECG-based ones needing a small implant to measure brain activity.

In both cases, larger studies are needed for a final assessment of their performances and to evaluate the loss of accuracy in real-life in patients affected by other metabolic disorders that can disturb the ECG- or EEG-based detection algorithms.

Finally, other techniques have been considered in this review. Breath-based detection is one of them, previously known through diabetes alert dogs. A prototype device was developed

for point-of-care testing with a good accuracy, but it seems difficult to imagine how such a technique and devices based on it could be used in real-life for continuous evaluation. NIR spectroscopy, alone or combined with other techniques, has also been used to generate hypoglycaemia alarms. It also stands amongst the candidates for noninvasive glucose monitoring, which could become in the future a good alternative.

Some other fluids like tears, sweat, urine or saliva are other milieus usable for blood glucose estimation, using the fluids' glucose correlation with blood glucose variations. However, the large lag-time between glucose variations in these fluids and in blood makes them less suitable candidates for hypoglycaemia detection. Thus, they are not detailed in this review. For further reading on these alternative modes of noninvasive and minimally invasive glucose monitoring, we recommend some recent reviews.^{30,31}

However, these technologies for the detection of hypoglycaemia cannot be proposed alone to patients, but have to be accompanied with a global strategy and plan of action to unveil their full potential in clinical practice. A recent report¹⁶² highlighted the utmost importance of therapeutic education programs to help patients recognise hypoglycaemia events, know the effects of their medications and activities, and how to appropriately correct a detected hypoglycaemia. Medications may also have to be adapted in some cases depending on the type of diabetes, for physical activities and for specific situations like religious fasting. This education and medication management is essential to reduce hypoglycaemic risks, before implementing the appropriate tool or device that will assist the patient.

7 | CONCLUSION

This extensive review presented a broad panel of devices and technologies related to hypoglycaemia detection and prediction techniques. PwD will almost certainly benefit from the next generation of CGM devices that will likely embed mid-term or long-term prediction features along with better accuracy and Se to glucose variations.

We believe other techniques and devices will struggle to compete with CGM devices in the near future as they are limited to event detection, and cannot inform PwD about their actual glucose levels. As such, they require reduced costs and acceptability related to noninvasive use to be successful.

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CONFLICT OF INTERESTS

Omar Diouri, Monika Cigler and Martina Vettoretti reports no conflict of interests. Julia K. Mader is co-founder and shareholder of decide Clinical Software GmbH. Julia K. Mader is a member in the advisory board of Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Dexcom, Eli Lilly, MSD, NovoNordisk A/S, Roche Diabetes Care, Sanofi, Servier and Takeda. Eric Renard reports consulting services to Abbott, Air Liquide SI, Cellnovo, Dexcom, Eli-Lilly, Insulet, Johnson & Johnson (Animas, LifeScan), Medirio, Medtronic, Novo-Nordisk, Roche and Sanofi and research support from Abbott, Dexcom, Insulet, Roche et Tandem. Pratik Choudhary has received speaker and consultancy fees from Novo Nordisk, Sanofi, Lilly, Insulet, Medtronic, Abbott, Diabits, Novartis and research support from Medtronic, Abbottm, Novo Nordisk and Dexcom.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of this review, and to the critical appraisal of content, and have read and approved the final version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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