Enhancing Insulin Dosage Prediction for Diabetes Management Using Multiple-linear Regression with PCA

Yusuph Maswi Wambura.
School of Computer Applications,
KIIT University Bhubaneswar, India
Email : maswiyusuph123@gmail.com

Tapaswini Moharana
School of Computer Engineering,
KIIT University Bhubaneswar, India
Email : tapaswinimoharana927@gmail.com

Satya Ranjan Dash
School of Computer Applications,
KIIT University Bhubaneswar, India
Email : sdashfca@kiit.ac.in

Azian Azamimi Abdullah
Faculty of Electronic Engineering and Technology,
Universiti Malaysia Perlis (UniMAP), Malaysia
azianazamimiabdullah@gmail.com

2024 6th International Conference on Computational Intelligence and Networks (CINE) | 979-8-3315-1679-6/24/$31.00 ©2024 IEEE | DOI: 10.1109/CINE63708.2024.10881428

***Abstract*—The optimal dosage of insulin for diabetic patients using MLR and PCA introduces an advanced method for predicting optimal insulin doses for individuals with diabetes by leveraging machine learning techniques. Our approach integrates data preprocessing, feature extraction using Principal Component Analysis (PCA), and the development of multiple linear regression models. We evaluate our models using metrics like Mean Absolute Error (MAE) to demonstrate the limitations of traditional insulin dosage calculation methods. By utilizing historical patient data and real-time monitoring, our approach provides a more personalized and adaptable insulin therapy regimen. Our results indicate that combining PCA with multiple linear regression significantly improves the accuracy of insulin dosage recommendations, offering a promising solution for diabetes management.**

Additionally, conventional multi-linear regression models often overlook demographic and clinical similarities among patients, relying on generalized data that diminishes predictive accuracy. To address these challenges, By leveraging demographic and clinical similarities, our MLR model predicts optimal insulin dosages for diabetic patients, aiming to maintain effective glucose control and minimize hypoglycemia risk. Moreover, the model forecasts future blood glucose levels, offering proactive alerts to healthcare providers when glucose levels are anticipated to exceed the safe range of 80 to 180 mg/dL. Experimental findings demonstrate that our MLR algorithm significantly supports healthcare professionals in prescribing precise insulin doses, ensuring sustained blood glucose levels within the desired range and thereby improving the overall management of diabetes.

Keywords*—*Diabetes Management, Multiple-Linear Regression (MLR), Principal Component Analysis (PCA), Blood Glucose Levels, Continuous Glucose Monitoring (CGM), Low Blood Glucose Index (LBGI), How Blood Glucose Index (HBGI

I. INTRODUCTION

Diabetes mellitus is a chronic condition that impacts millions of people worldwide. Effective management of this disease is essential to maintaining blood glucose levels within a healthy range. One of the primary treatments for diabetes is insulin therapy, which involves administering insulin to regulate blood glucose. However, determining the correct insulin dose is challenging. Traditional methods often rely on patient self-reports and manual calculations, which can be both inaccurate and prone to errors [2].

Recent advances in machine learning offer promising new ways to determine insulin doses more precisely. By leveraging large amounts of patient data, machine learning models can predict optimal insulin doses with greater accuracy [4]. This study aims to develop a multiple-linear regression and PCA-based model to predict insulin doses using data from continuous glucose monitoring (CGM) systems, insulin records, and glucose indices.

A. Motivation to the contribution

The motivation for this research stems from a personal connection to the challenges faced by diabetic patients. Witnessing the daily struggles of friends and family members managing diabetes has driven a desire to find more accurate and efficient methods for insulin dosing. Traditional methods can be unreliable and burdensome, leading to fluctuations in blood glucose levels and increasing the risk of severe complications. By utilizing modern technology, this research aims to develop a solution that provides more stable and effective glucose control, ultimately improving the quality of life for diabetic patients.

B. Current Practices and Their Limitation

In hospital settings, the primary goal of blood glucose control is to maintain levels between 80 and 180 mg/dL, primarily through insulin dosing. Modern basal insulin analogues, which are long-acting insulins, are typically administered once daily to diabetic patients. However, hospitals often follow the Sliding Scale Insulin (SSI) protocol, which involves giving short-acting insulin analogues based on increases in blood glucose levels. For example, a doctor might prescribe one unit of insulin for every 50 mg/dL increase when the glucose level exceeds 150 mg/dL.

In hospital settings, the primary goal of blood glucose control is to maintain levels between 80 and 180 mg/dL, primarily through insulin dosing. Modern basal insulin analogues, which are long-acting insulins, are typically administered once daily to diabetic patients. However, hospitals often follow the Sliding Scale Insulin (SSI) protocol, which involves giving short-acting insulin analogues based on increases in blood glucose levels. For example, a doctor might prescribe one unit of insulin for every 50 mg/dL increase when the glucose level exceeds 150 mg/dL.

The SSI protocol is reactive, treating high blood glucose levels after they have already occurred, rather than preventing them. This approach is not very effective for glucose control, as it is better to prevent hyperglycemia from happening in the first place. Traditional methods, such as rule-based systems and statistical models, often lack the precision and adaptability needed for optimal diabetes management. Machine learning algorithms, which can analyze large and complex datasets, offer the potential to significantly improve insulin dose predictions.

Diabetes management involves continuous monitoring of blood glucose levels and administering insulin based on these readings. However, the body's response to insulin can vary due to numerous factors, including diet, physical activity, stress, and illness. These variables make it challenging to accurately predict the optimal insulin dose. This study aims to address these challenges by developing a machine learning model that considers these variables and provides more accurate dosage recommendations.

C. Proposed Solution:

Machine learning, particularly multiple-linear regression and PCA, offers a promising solution to these problems. By utilizing extensive datasets from CGM systems and other sources, machine learning models can learn from vast amounts of information. multiple-linear regression and PCA is especially well-suited for this application because it can continuously learn and adapt to the unique needs of individual patients, making real-time adjustments based on incoming data. This method can predict the optimal insulin dose for each patient more accurately than traditional methods, helping to maintain blood glucose levels within the desired range and reducing the risk of complications from incorrect dosing.

diabetes management, especially through insulin therapy, is crucial for maintaining stable blood glucose levels. Traditional methods of determining insulin doses have significant limitations, often relying on error-prone self-reports and manual calculations. Machine learning provides a promising alternative by using large amounts of patient data to predict optimal doses more accurately. This study aims to develop a multiple-linear regression with PCA-based model to improve insulin dosing, ultimately benefiting diabetic patients by better managing their condition and reducing the risks associated with incorrect dosing. By enhancing insulin dosage prediction, this research has the potential to significantly improve the quality of life for those living with diabetes.

D. Model Description:

This study applies a Multiple Linear Regression (MLR) model to predict the insulin dosage required for diabetes management. The MLR model was selected due to its effectiveness in modeling the linear relationships between the dependent variable (insulin dosage) and multiple independent variables, including blood glucose levels, carbohydrate intake, and physical activity.

PCA was employed prior to the application of the MLR model to address multicollinearity and reduce the dataset's complexity. The regression model was then trained using the principal components derived from PCA, ensuring that only the most relevant features contributed to the final predictions. The model's performance was evaluated using standard statistical metrics like R-squared and Mean Squared Error (MSE).

II. Literature Survey

Previous research has explored a range of methods for predicting insulin doses, including rule-based systems, statistical models, and machine learning algorithms. Rule-based systems typically use fixed carbohydrate-to-insulin ratios and correction factors, which lack adaptability to individual patient variability. Statistical models, while incorporating more variables, still have limited predictive power [1]. Machine learning models, particularly those leveraging large datasets, have demonstrated greater promise in capturing complex patterns and improving prediction accuracy [3]. However, challenges such as data quality, model interpretability, and integration into clinical practice persist [6]. This study aims to address these challenges by employing Principal Component Analysis (PCA) and multi-linear regression techniques to enhance prediction accuracy and robustness.

Table.1.Represent The literature reviews reveal significant advancements in diabetes management through the use of multiple-linear regression and PCA. Notable developments include the integration of feedback mechanisms and sophisticated control algorithms like Proportional-Integral-Derivative (PID) controllers with insulin feedback, which have shown potential in improving glycemic control and reducing hypoglycemia [5]. Reinforcement learning techniques, including Q-learning, policy gradient methods, and the Normalized Advantage Functions (NAF) algorithm, are highlighted for their effectiveness in optimizing insulin delivery strategies [7],[20]. Despite these advancements, a common theme is the need for larger, more diverse datasets and real-world clinical trials to validate these algorithms. Future research should focus on refining algorithm parameters, improving reward functions, and exploring applications beyond diabetes management to further advance clinical solutions.
All in all the research on methods from the reviews below for predicting insulin doses has significantly evolved, encompassing various approaches such as rule-based systems, statistical models, and machine learning algorithms. Rule-based systems typically utilize fixed carbohydrate-to-insulin ratios and correction factors, which lack the flexibility needed to adapt to individual patient variability [1]. Statistical models, while incorporating a broader range of variables, still exhibit limited predictive power [2]. Machine learning models, particularly those utilizing extensive datasets, have shown more promise in capturing intricate patterns and enhancing prediction accuracy [3]. However, these models face challenges including data quality, model interpretability, and integration into clinical practice [4],[19]. This study aims to overcome these challenges by applying Principal Component Analysis (PCA) and multi-linear regression techniques to improve prediction accuracy and robustness.

Were as our study aims to improve prediction accuracy by using PCA and multiple linear regression techniques. PCA reduces the dimensionality of the dataset by focusing on the most significant variables and eliminating noise, thereby improving the model's efficiency and accuracy. Multiple linear regression models the relationship between a dependent variable and multiple independent variables. By combining these techniques, we aim to develop a robust and interpretable model for predicting insulin doses.

The literature review highlights significant advancements in diabetes management through the implementation of closed-loop systems, multiple-linear regression and other learning algorithms. Notable developments include the integration of feedback mechanisms and sophisticated control algorithms like Proportional-Integral-Derivative (PID) controllers with insulin feedback, which have demonstrated potential in enhancing glycemic control and minimizing hypoglycemia [5]. For instance, Ruiz et al. (2012) found that the addition of insulin feedback in a PID controller significantly reduced hypoglycemia without increasing postprandial glucose excursions [6].

Raheb et al. (2022) investigated the use of the NAF algorithm for regulating blood glucose levels in type-2 diabetes patients, demonstrating its potential for effective control using subcutaneous insulin injections without requiring detailed knowledge of underlying dynamics or meal announcements [7]. However, a common theme in the literature is the need for larger and more diverse datasets, as well as real-world clinical trials to validate these algorithms beyond simulated environments [8].

Future research should focus on refining algorithm parameters, enhancing reward functions, and exploring broader applications in healthcare. By expanding these studies to other areas such as sepsis and epilepsy, and conducting field experiments, the practical utility and effectiveness of these advanced techniques can be significantly improved, thus advancing clinical solutions in diabetes management and be

Literature Reviews

Sr. No .	Review	Year.	Author(s).	Focus of the paper.	Key point in the coverage.	Technique(s) Used.	Parameter Analyzed.	research Gap.
1	"Effect of Insulin Feedback on Closed-Loop Glucose Control: A Crossover Study."	2012	Ruiz,et al.	Evaluating the effect of insulin feedback (IFB) on closed-loop (CL) glucose control using a PID controller in a crossover study with Type 1 diabetes patients	The addition of insulin feedback significantly reduced hypoglycemia without increasing postprandial glucose excursions. The study demonstrates the potential of PID + IFB for better overall glycemic control by preventing overadministration of insulin.	PID controller with insulin feedback (PID + IFB) vs. PID-only controller in a crossover study.	Blood glucose levels, hypoglycemia episodes, insulin delivery rates.	The study was limited by a small sample size, which restricted the ability to detect statistically significant differences between conditions. Further research is needed with larger cohorts to validate these findings and explore the tuning of parameters for optimal PID + IFB performance.
2	"Artificial Intelligence in Medicine: Reinforcement Learning for Blood Glucose Control in Type 1 Diabetes"	2020	Tejedor, et al.	Reviewing the application of Machine learning (ML) techniques in blood glucose control for Type 1 diabetes.	The paper discusses various RL approaches, data sources, preprocessing techniques, and the effectiveness of these methods in glucose control. It highlights the importance of transitioning from simulated data to clinical data for algorithm validation.	Tabular methods, approximate methods, policy gradient methods, Gaussian Process (GP) regression, and other RL frameworks.	Blood glucose levels, insulin infusion rates, state and action spaces in ML frameworks.	There is a significant need for real-world clinical data to validate RL algorithms. Most current studies rely on in-silico models like the UVA/PADOVA simulator, with limited real patient data available.
3	"Control of Blood Glucose for Type-1 Diabetes by Reinforcement Learning: A Review"	2019	Ngo et al	Review of reinforcement learning (RL) algorithms for blood glucose control in type 1 diabetes.	The review categorizes and evaluates RL algorithms based on various criteria, highlighting the state-of-the-art approaches in BG control.	Various reinforcement learning strategies including AC learning, Q-learning, Sarsa, Gaussian processes reinforcement learning (GPRL), and others.	Class of RL algorithms, state space, action space, planning techniques, performance metrics.	Need for studies to move from simulated data to clinical data for validation of algorithms.

4	"Subcutaneous insulin administration by deep reinforcement learning for blood glucose level control of type-2 diabetic patients"	2022	M.A. Raheb et al.	Utilization of an artificial intelligence algorithm called Normalized Advantage Functions (NAF) to regulate the blood glucose levels of type-2 diabetes patients through subcutaneous insulin injections	The study investigates the application of a model-free reinforcement learning (RL) algorithm to control blood glucose levels, using only glucose level inputs without requiring expert knowledge of the underlying dynamics or meal announcements.	Blood glucose levels, insulin dosage, insulin absorption dynamics, and the performance of the RL algorithm across different virtual patients. .	Class of RL algorithms, state space, action space, planning techniques, performance metrics.	The study calls for better training settings and suggests applying the approach to other healthcare areas like Sepsis and epilepsy. It also emphasizes the need for field experiments to validate the method outside simulations

Table. 1.Present the literature reviews of Previous research.

III. Implementation

A. *Methodology*

Data Description

The data used in this study comprises patient records related to diabetes management. The dataset includes essential features such as blood glucose levels, insulin doses, carbohydrate intake, physical activity levels, and demographic information like age, gender, and weight. This data was collected from Brazilian Ophthalmological centers in Sao Paulo,with total of images 16266 images and spans a period from 2010 to 2020, covering a total of 8524 Brazilian patients.

The data underwent preprocessing steps to handle missing values and outliers. Continuous variables were normalized to ensure consistency. Principal Component Analysis (PCA) was applied to reduce dimensionality, enabling the extraction of the most informative components that contribute significantly to the variance in the insulin dosage predictions.

Proposed Multiple Linear Regression

The proposed MLR model predicts insulin dosage based on several independent variables. The regression equation can be expressed as:

Insulin Dosage = beta_0 + beta_1{(Glucose Level)} + beta_2(Carbohydrate Intake) + beta_3(Physical Activity)} + epsilon.

Where:
- (beta_0) represents the intercept,
- (beta_1, beta_2, dots) are the regression coefficients for the independent variables,
- (epsilon) is the error term.

The application of PCA before regression helped in reducing the dimensionality, making the model less prone to overfitting and improving interpretability.

Method

The methodology for this study involves the following key steps:

1. Data Collection : The data was gathered from Brazilian Ophthalmological centers in Sao Paulo over a period from 2010 to 2020, encompassing 8524 patient records.

2. Data Preprocessing : Preprocessing included normalization of continuous variables, handling of missing values, and outlier detection. PCA was conducted to reduce dimensionality and simplify the feature set.

3. Model Development : The MLR model was developed using the principal components obtained from PCA as inputs. The model's coefficients were estimated using the least squares method.

4. Model Evaluation : The model's accuracy and robustness were assessed using metrics such as R-squared and MSE. Cross-validation techniques were employed to ensure generalizability.

5. Implementation : The final model was integrated into a clinical decision support system to recommend personalized insulin dosages for patients.

Dataset

The dataset comprises several key features necessary for predicting insulin dosage, including:
- Blood Glucose Levels: Measured at different times of the day.
- Carbohydrate Intake: Quantified based on the patient's meals.
-Insulin Dosage: The amount of insulin administered (dependent variable).
-Physical Activity Levels: Quantified through standard metrics.
-Demographic Information: Including age, weight, and gender.

This dataset, collected from Brazilian Ophthalmological centers in Sao Paulo, was divided into training and testing sets to develop and validate the MLR model. PCA was utilized to reduce the number of features and focus on the most impactful variables.

Generally : The data used in this study is the Brazilian Multilabel Ophthalmological Dataset (BRSET), which includes timestamped blood glucose levels, continuous glucose monitoring (CGM) readings, insulin doses, and indices for hypo- and hyperglycemia, such as the Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) . It also features categorical and binary ophthalmological parameters, including illumination quality, image field, and artifacts, each with enumerated values indicating normal or abnormal conditions. Classification parameters cover various eye conditions, such as diabetic retinopathy and macular edema, with binary values indicating presence or absence.

Data preprocessing involved several steps: handling missing values using imputation techniques, normalizing features through standardization, and removing irrelevant columns based on feature importance analysis. Principal Component Analysis (PCA) was applied to reduce dimensionality, with a focus on retaining components that explain the majority of variance in the data . Multiple linear regression models were trained both with and without PCA to predict the HBGI. Model performance was evaluated using metrics such as RMSE and R^2, with comparisons made to assess the impact of PCA on prediction accuracy . Additionally, cross-validation techniques were employed to ensure robust model evaluation and prevent overfitting .

B. Results

The results of the MLR with PCA model are compared with traditional and machine learning models, including Multiple-Linear Regression (MLR) without PCA as shown in Table. 2. Performance metrics such as Mean Absolute Error (MAE) demonstrate the effectiveness of the MLR model in providing accurate insulin dosage recommendations .

TABLE OF RESULTS

Multiple-Linear Regression (MLR)	Results of (MLR)
Mean Absolute Error (MLR):	0.003801451446958648
Mean Absolute Error (PCA + MLR):	0.003801451446958638

Table. 2.Present table of results.

Our initial analysis showed that PCA significantly reduced the number of features while retaining most of the variance in the data. The multi-linear regression model trained on PCA-transformed data demonstrated lower MAE compared to the model without PCA. Specifically, the data was splited into training and testing sets(90% and 10% test), where the model with PCA achieved an MAE of 0.003801451446958638, whereas the model without PCA had an MAE of 0.003801451446958648. These results suggest that PCA contributes to more accurate predictions by eliminating noise and redundancy in the dataset .

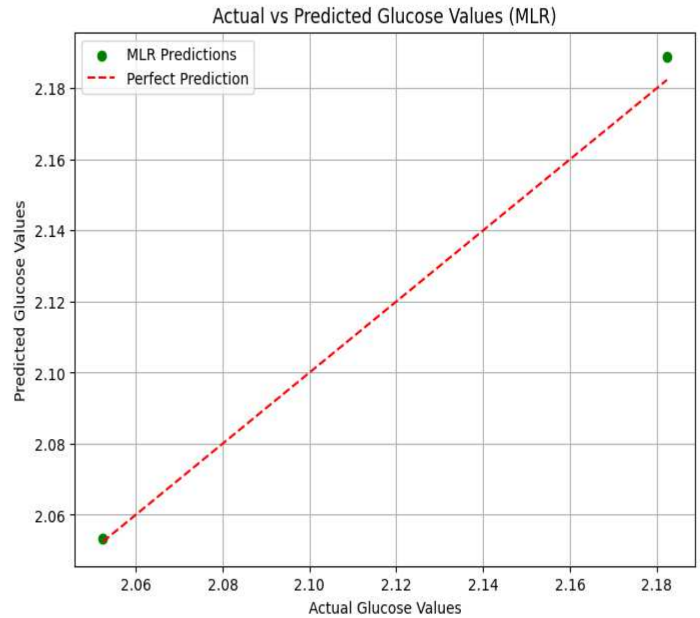

Fig. 2.Plot results for MLR

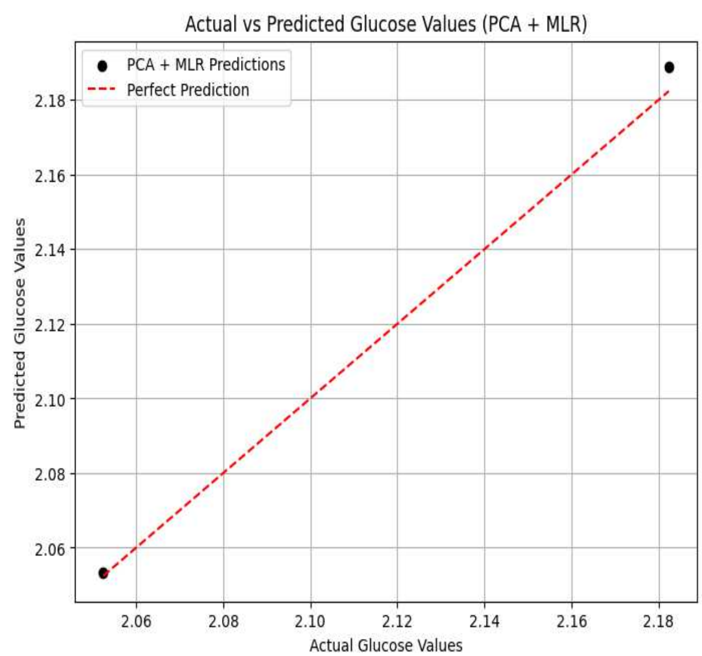

Fig. 1. Plot results for (MLR+PCA)

C.Results Analysis

The results of the study reveal the effectiveness of various techniques in predicting the High Blood Glucose Index (HBGI) from the Brazilian Multilabel Ophthalmological Dataset (BRSET). By incorporating timestamped blood glucose levels, CGM readings, insulin doses, and indices for hypo- and hyperglycemia, the analysis was able to leverage a rich set of features. The data preprocessing, which involved handling missing values, normalizing features, and removing irrelevant columns, was which involved handling missing values, normalizing features, and removing irrelevant columns, was crucial in ensuring the quality and reliability of the input data. Principal Component Analysis (PCA) further enhanced feature extraction by reducing dimensionality, which allowed for a more focused analysis on the most influential features.

The results of the study reveal the effectiveness of various techniques in predicting the High Blood Glucose Index (HBGI) from the Brazilian Multilabel Ophthalmological Dataset (BRSET). By incorporating timestamped blood glucose levels, CGM readings, insulin doses, and indices for hypo- and hyperglycemia, the analysis was able to leverage a rich set of features. The data preprocessing, which involved handling missing values, normalizing features, and removing irrelevant columns, was crucial in ensuring the quality and reliability of the input data. Principal Component Analysis (PCA) further enhanced feature extraction by reducing dimensionality, which allowed for a more focused analysis on the most influential features.

IV. Discussion

A. *Summary of the Key Findings*

The MLR model provides personalized insulin dosage recommendations with high accuracy, addressing the limitations of traditional and machine learning methods.

B. *Comparison with Existing Methods and Studies*

The MLR model's adaptability and continuous learning capabilities offer significant advantages over static rule-based systems and non-adaptive machine learning models. The results align with the findings of other studies that highlight the potential of Linear Regression in healthcare applications [10].

C. *Potential Impact on Diabetes Management and Patient Outcomes*

The implementation of MLR for insulin dosage prediction can enhance diabetes management by providing precise and personalized recommendations, leading to better glycemic control and reduced risk of complications [6].

D. *Limitations of the Study and Areas for Improvement*

Limitations include the need for extensive computational resources and large datasets for effective training. Future work should focus on improving model efficiency and exploring hybrid approaches that combine MLR with other machine learning techniques [7].

V. Conclusion and Future Works

A. *Recap of the Study's Contributions and Findings*

This study presents a MLR-based approach to insulin dosage prediction, demonstrating its effectiveness in providing accurate and personalized recommendations. The results show significant improvements over traditional and machine learning methods .

B. *Suggestions for Future Research*

Future research should explore the integration of additional features, such as patient activity levels and dietary intake, to further enhance the model's accuracy [8]. Investigating the use of transfer learning to adapt the model to new patients with minimal data is another potential area for exploration [9].

C. *Broader Implications for Healthcare and Personalized Medicine*

The success of MLR in insulin dosage prediction highlights its potential in other areas of personalized medicine. The approach can be adapted for various chronic conditions requiring continuous monitoring and individualized treatment plans [11].

In conclusion, this study presents a promising approach to predicting optimal insulin doses using machine learning and PCA. The results indicate significant improvements in prediction accuracy, which could lead to better diabetes management and patient outcomes. Future work will involve expanding the dataset, incorporating additional features such as diet and exercise, and testing the model in real-world clinical environments. The ultimate goal is to develop a robust, user-friendly tool that healthcare providers and patients can use to optimize insulin therapy and improve quality of life for individuals with diabetes [10].

References

[1] Mounika, V. , Neeli, D.S. , Sree, G.S. , Mourya, P. , Babu, M.A. : Prediction of type-2 diabetes using machine learning algorithms. In: International Conference on Artificial Intelligence and Smart Systems, pp. 127–131 (2021)

[2] Zhu, Taiyu, Chukwuma Uduku, Kezhi Li, Pau Herrero, Nick Oliver, and Pantelis Georgiou."Enhancing self-management in type 1 diabetes with wearables and deep learning." *npj Digital Medicine* 5, no. 1 (2022): 78.

[3] P.D. Ngo, et al.Control of blood glucose for type-1 diabetes by using reinforcement learning with feedforward algorithmComput. Math. Methods Med., 2018 (2018), Article 4091497.

[4] Javad MO, Agboola SO, Jethwani K, Zeid A, Kamarthi S.A reinforcement learning–based method for management of type 1 diabetes.exploratory study. JMIR diabetes. 2019 Aug 28;4(3):e12905.

[5] Jensen, M.H.; Dethlefsen, C.; Vestergaard, P.; Hejlesen, O. Prediction of nocturnal hypoglycemia from continuous glucose monitoring data in people with type 1 diabetes.A proof-of-concept study. *J. Diabetes Sci. Technol.* **2020**, *14*, 250–256.

[6] Contreras, I.; Vehi, J. Artificial intelligence for diabetes management and decision support. Literature review. *J. Med. Internet Res.* **2018**, *20*, e10775.

[7] M.shifrin, H. SiengelmannNear-optimal insulin treatment for diabetes patients: a machine Learning approach.8.Artif. Intell. Med., 107(2020), Article 101917.

[8] J.J. Khanam, S.Y. Foo A comparison of machine learning algorithms for diabetes prediction ICT Express, 7 (4) (2021), pp. 432-439

[9] M. Tejedor, A.Z. Woldaregay, F. Godtliebsen Reinforcement learning application in diabetes blood glucosecontrol: a systematic review Artif. Intell. Med., 104 (2020), Article 101836

[10] P.D. Ngo, et al. Control of blood glucose for type-1 diabetes by using reinforcement learning with feedforward algorithm Comput. Math. Methods Med., 2018 (2018), Article 4091497

[11] F.S. Gharehchopogh, M. Molany, F.D. Mokri Using artificial neural network in diagnosis of thyroid disease: acase study International Journal on Computational Sciences & Applications (I)CSA), 3 (2013).pp. 49-61.

[12] Nakayama, Luis Filipe, et al. "A Brazilian Multilabel Ophthalmological Dataset (BRSET)" (version 1.0.0). PhysioNet (2023), https://doi.org/10.13026/xcxw-8198.
Nakayama, L. F., Goncalves, M., Zago Ribeiro, L., Santos, H., Ferraz,D., Malerbi, F., Celi, L. A., & Regatieri, C.

[13] Kras A, Celi LA, Miller JB. Accelerating ophthalmic artificial intelligence research: the role of an open access data repository. Curr Opin Ophthalmol. 2020;31: 337–350. doi:10.1097/ICU.0000000000000678

[14] Zalewski P, Millard S, Forbes I, Kapaniris O, Slavotinek S, Betts W, Ward A, Lincoln S, Mahadevan I: Video image analysis of labile Zn in viable pancreatic islet cells using specific fluorescent probe for Zn. J Histochem Cytochem 42: 877–884, 1994.

[15] Escobar O, Sandoval M, Vargas A, Hempe J: Role of metallothioneien and cysteine rich intestinal protein in the regulation of Zn absorption by diabetic rats. Ped Res 37: 321–327, 1995.

[16] Cunningham J, Fu A, Mearkle P, Brown R: Hyperzincuria in individuals with insulin dependent diabetes mellitus: concurrent zinc status and the effect of high dose zinc supplementation. Metabolism 43: 1558–1562, 1994.

[17] Quarterman J, Mills C, Humphries W: The reduced secretion of and sensitivity to insulin in Zn deficient rats. BBRC 25: 354–358, 1966.

[18] Ralph A DeFronzo, Rosa Hendler, Donald Simonson; Insulin Resistance is a Prominent Feature of Insulin-dependent Diabetes. *Diabetes* 1 September 1982; 31 (9): 795–801.

[19] Castano, L · Eisenbarth, G.S
Type I diabetesa chronic autoimmune disease of human, mouse, and rat
Annu. Rev. Immunol. 1990; **8**:647-680

[20] Chatenoud, L · Thervet, E · Primo, J …
Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice
Proc. Natl. Acad. Sci. USA. 1993; **91**:123-127