

Machine Learning-driven Identification of the Honeymoon Phase in Pediatric Type 1 Diabetes and Optimizing Insulin Management

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What is already known on this topic?

The honeymoon phase in type 1 diabetes (T1D) is characterized by a temporary period of reduced insulin needs and better glucose control. Current methods for identifying this phase rely on clinical observations, but they lack precision and often result in delayed or suboptimal insulin management.

What this study adds?

This study introduces advanced machine learning models, such as long short-term memory networks and transformer models, to accurately detect the honeymoon phase in T1D patients. By analyzing continuous glucose monitoring data, these models enhance the precision of honeymoon phase identification, leading to more personalized insulin management and improved overall glycemic control.

Abstract

Objective: The honeymoon phase in type 1 diabetes (T1D) represents a temporary improvement in glycemic control but may complicate insulin management. The aim was to develop and validate a machine learning (ML)-driven method for accurately detecting this phase to optimize insulin therapy and prevent adverse outcomes.

Methods: Data from pediatric T1D patients aged 6-17 years, including continuous glucose monitoring data, glucose management indicator (GMI) reports, hemoglobin A1c (HbA1c) values, and patient medical history, were used to train ML models including long short-term memory (LSTM) networks, transformer models, random forest, and gradient boosting machines (GBMs). These were designed to analyze glucose trends and identify the honeymoon phase in T1D patients.

Results: The transformer model achieved the highest accuracy at 91 %, followed by GBMs at 89 %, LSTM at 88 %, and random forest at 87 %. Key features, such as glucose variability, insulin adjustments, GMI values, and HbA1c levels were critical to model performance. Accurate identification of the honeymoon phase enabled optimized insulin adjustments, enhancing glucose control and reducing hypoglycemia risk.

Conclusion: The ML-driven approach provides a robust method for detecting the honeymoon phase in T1D patients, demonstrating potential for improved personalized insulin management. The findings suggest significant benefits in patient outcomes, with future research focused on further validation and clinical integration.

Keywords: Honeymoon phase, insulin management, machine learning, type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a chronic autoimmune condition characterized by the destruction of insulin-producing

beta cells in the pancreas, leading to lifelong dependence on exogenous insulin therapy (1,2). The honeymoon phase is a well-recognized but transient period following the initial diagnosis of T1D, where patients experience a

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temporary remission of symptoms and improved glycemic control (3,4,5). During this phase, the body retains some residual insulin secretion, reducing the exogenous insulin requirements and stabilizing blood glucose levels. This phase can last from a few months to over a year and varies significantly between patients (6).

However, the honeymoon phase also presents a clinical challenge, as fluctuating insulin needs complicate management strategies, leading to a higher risk of both hypoglycemia and hyperglycemia if not accurately detected and managed (Figure 1) (7). The honeymoon phase is quantified based on significant reductions in insulin requirements, typically defined as a 20-30% decrease in the insulin dose over a 3-6-month period, along with a stable or improving trend in blood glucose levels. Moreover, glucose variability is measured by analyzing the standard deviation of continuous glucose monitoring (CGM) readings during this period (8).

Accurate detection of the honeymoon phase is important for optimizing insulin therapy. Early identification enables healthcare providers to adjust dosages precisely, potentially prolonging the phase and improving patient outcomes (9). Traditional detection methods, such as clinical judgment and periodic hemoglobin A1c (HbA1c) monitoring (Figure 2), often lack the precision required to capture nuanced fluctuations in glucose levels, leaving a gap in timely and effective management (10,11,12).

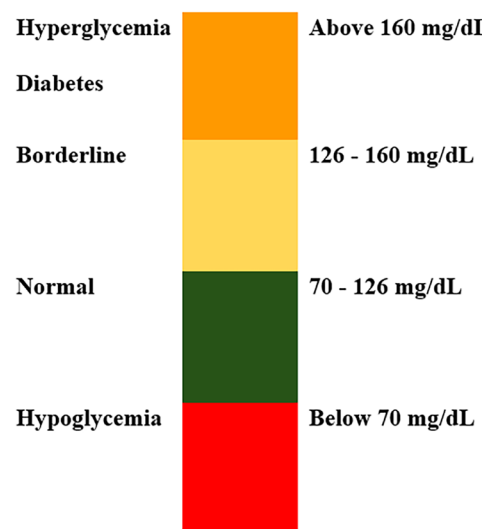


Figure 1. Glucose levels classification

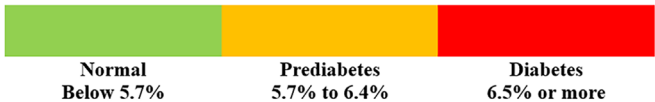


Figure 2. A1c levels for diagnosing diabetes

Recent advances in machine learning (ML) techniques offer a promising alternative by leveraging large datasets to uncover patterns not apparent through conventional methods (13,14,15). ML has already demonstrated significant potential in diabetes management, including predicting glucose trends, optimizing insulin delivery, and personalizing treatment strategies (16,17,18,19,20). For instance, transformer models and long short-term memory (LSTMs) networks have been employed to predict glucose variability, while reinforcement learning approaches have facilitated personalized insulin dosing strategies using CGM data (21,22). ML applications are also being explored for predicting hypoglycemic events and enhancing artificial pancreas systems (23,24).

This study focused on applying ML modeling to identify the honeymoon phase in T1D patients, an area that remains largely unexplored in prior research. By employing algorithms such as LSTM networks, transformer models, random forest, and gradient boosting machines (GBMs), the proposed approach aims to overcome the limitations of traditional techniques (25,26,27). The analysis relied on a comprehensive dataset comprising CGM data, glucose management indicator (GMI) reports, HbA1c values, and patient medical history, which add credibility and robustness to the study (28,29).

Building on previous work, this study uniquely addresses the honeymoon phase using a data-driven framework. Early and accurate detection has the potential to personalize insulin therapy, reduce glycemic variability, and extend the duration of partial remission, ultimately improving long-term outcomes for T1D patients.

Methods

The dataset for this study was sourced from multiple clinical sites, encompassing a diverse range of T1D patient profiles. Each site contributed de-identified data to ensure patient confidentiality and adherence to ethical standards. By aggregating data from various clinical settings, the study captured a comprehensive array of patient experiences and glucose management scenarios, facilitating a robust analysis of the honeymoon phase in T1D (30). This approach not only enhanced the generalizability of the findings but also upheld rigorous ethical practices by anonymizing patient information throughout the data collection and analysis processes (31). The dataset, which included information from the Kaggle platform, further supports this by providing a rich resource for developing and validating ML models aimed at optimizing insulin management and identifying the honeymoon phase in T1D pediatric patients (32,33).

Data Collection

CGM devices were calibrated against a standard glucose meter to ensure accuracy before data collection. Patients wore the devices continuously, typically on the upper arm or abdomen, providing real-time glucose monitoring. Data was transmitted securely to a server, with encryption and backups ensuring data integrity and patient confidentiality. High-resolution glucose measurements were recorded every 5 minutes, with monthly GMI reports summarizing long-term control. Patient medical history, including demographics, insulin regimens, and historical glucose data, was comprehensively documented to support detailed analysis (34).

In addition to clinical data, a publicly available, anonymized diabetic dataset from Kaggle was used to validate ML models. This supplemental dataset provided additional diversity in glucose trends and patient characteristics, aimed at enhancing the robustness of the analysis. The combined dataset included 150 pediatric T1D patients, with an age range of 6 to 17 years.

The CGM system recorded glucose levels in the interstitial fluid at regular intervals, providing a comprehensive view of glucose fluctuations over time. Each 24-hour period yielded between 96 and 288 data points, critical for analyzing short- and long-term glycemic control (35). Day-wise GMI reports monitored glucose levels and identified hypoglycemic events, focusing on readings below 70 mg/dL, as shown in Figure 3. This data enabled accurate adjustments to insulin management strategies.

Insulin doses were adjusted based on real-time CGM data and day-wise GMI reports to optimize glucose control. The

adjustment protocol involved reducing doses when glucose levels fell below 70 mg/dL to prevent severe hypoglycemia. Conversely, doses were increased when glucose levels exceeded the target range or insulin needs changed due to meal times or physical activity (36).

To optimize glucose control during the study, insulin doses were adjusted using a structured approach based on real-time CGM data and the automated bolus suggestion (ABS) formula. The ABS formula, applied to each patient, accounts for current blood glucose levels, target glucose goals, insulin sensitivity, and carbohydrate intake.

HbA1c levels were monitored to reflect long-term glucose control by averaging blood glucose over the past two to three months. Comparing HbA1c trends with CGM data evaluated whether short-term insulin modifications improved long-term glycemic control. Regular HbA1c monitoring provided insights into the success of treatment strategies, with lower levels indicating better control and reduced risk of complications (37). Key features extracted included glucose levels, insulin doses, glucose variability, and hypoglycemic events, focusing on episodes where glucose fell below 70 mg/dL. GMI reports were also incorporated, offering monthly summaries that reflected long-term glucose control and trends. HbA1c values (38), reflecting the average blood glucose levels over the past two to three months (Figure 4), were used to validate the effectiveness of insulin adjustments and the overall glucose management strategy.

Ethical Considerations

Patient data were anonymized to protect confidentiality and comply with data protection regulations. Institutional Review Board approval was obtained for the use of patient

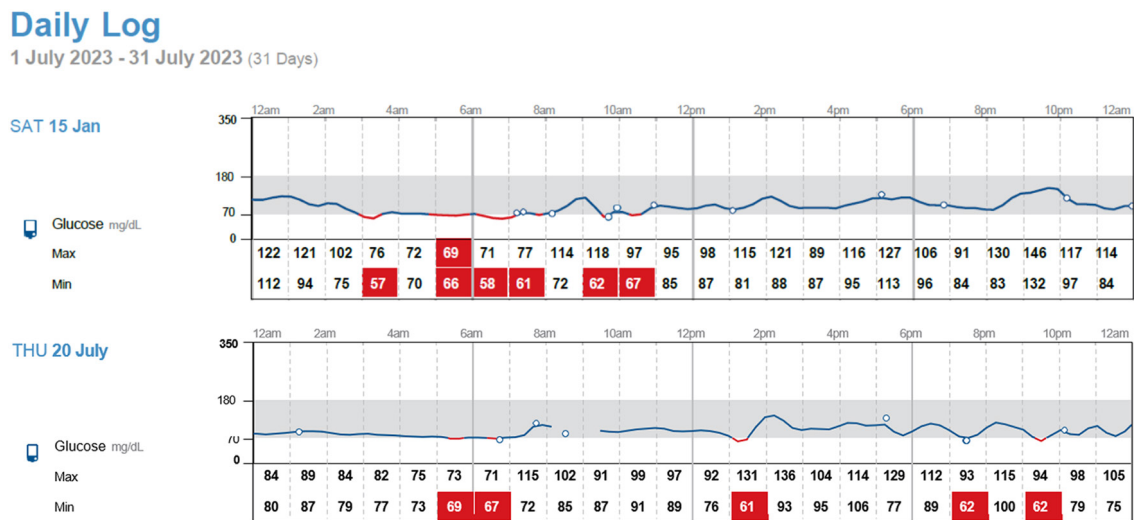


Figure 3. Day-wise glucose management indicator reports

Max.: maximum, Min.:minimum

data, and informed consent was acquired from the patient for the use of their data in this study. The dataset from Kaggle was used to supplement the analysis, which contains anonymized data from multiple patients with diabetes, and was used in compliance with ethical standards for secondary data analysis. The study was approved by the Narasaraopeta Engineering College: Narasaraopeta of Institutional Review Board (IEC ref. no: 01/2024, date: 28.08.2024).

Statistical Analysis

The statistical analysis for this study was conducted to evaluate the effectiveness of insulin dose adjustments and glucose management in identifying the honeymoon phase in pediatric T1D patients. Descriptive statistics, including

mean, median, standard deviation, and coefficient of variation, were calculated to summarize glucose levels and insulin doses over the study period. Temporal metrics, such as time-in-range, time-below-range, and time-above-range, were computed to assess glycemic control. Correlation analysis and linear regression were employed to examine the relationship between insulin doses and glucose levels, with statistical significance set at $p < 0.05$.

All statistical analyses were performed using R, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Additional data processing and visualization were conducted using Python (version 3.11.5) with the pandas and matplotlib libraries (Python Software Foundation, Wilmington, Delaware, USA).

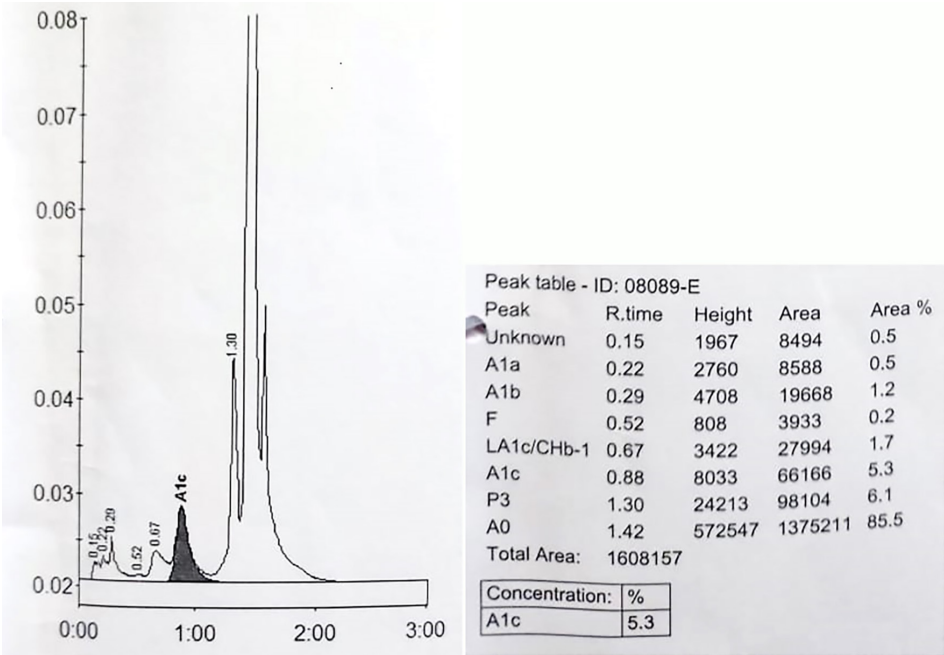


Figure 4. Longitudinal A1c report

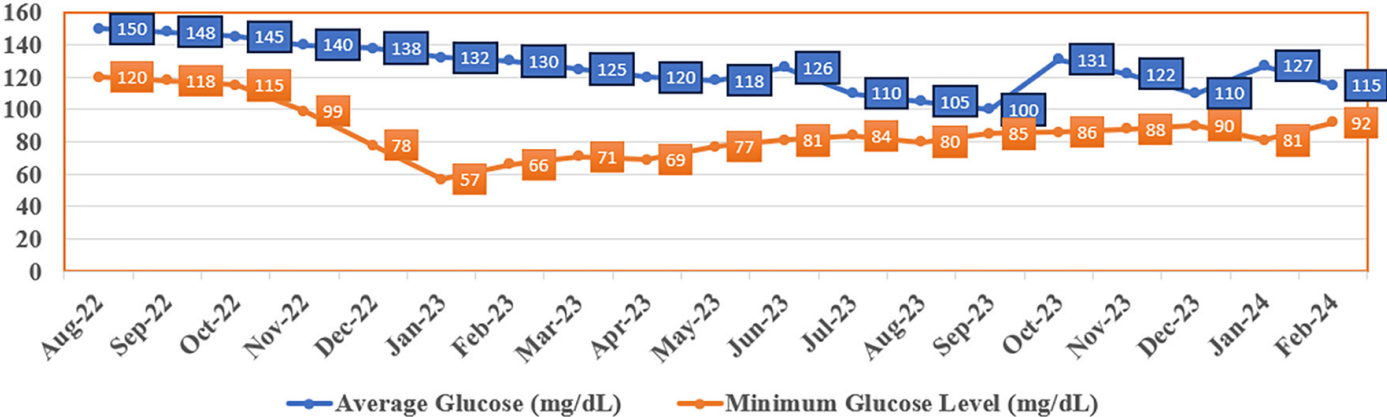


Figure 5. Glucose management indicator trends over time

Machine Learning Models

ML models were employed to enhance the identification of the honeymoon phase in T1D pediatric patients by analyzing data from CGM devices, insulin dosages, glucose variability, and hypoglycemic events. These models used advanced algorithms to detect patterns and trends indicative of the honeymoon phase, characterized by a temporary improvement in glycemic control and reduced insulin requirements (39,40).

Rationale for Model Selection

The selection of ML models in this study was based on the unique characteristics of the dataset and the challenges of detecting the honeymoon phase. LSTM networks were chosen for their ability to capture temporal patterns in sequential CGM data. Transformers, with their self-attention mechanisms, offer precision in identifying complex relationships between glucose data and insulin adjustments. Random forest classifiers were used for their robustness in handling noisy and diverse datasets, while GBMs were selected for their ability to iteratively improve prediction accuracy by identifying subtle patterns in glucose data. This combination of models ensures a comprehensive approach, taking advantage of each model's strengths to address the dataset's temporal, variable, and noisy nature (41).

LSTM networks were used for their ability to analyze time-series CGM data effectively, interpreting temporal patterns to identify significant glucose trends. LSTM memory cells and gating mechanisms allows a focus on relevant patterns while filtering out noise, optimizing insulin adjustments based on real-time glucose trends (21,42).

Transformers were applied to capture intricate patterns in glucose fluctuations and insulin adjustments using self-attention mechanisms. These models excel in preserving sequence order through positional encoding, enabling precise long-term trend interpretation and supporting personalized insulin management (25,43).

Random forest classifiers handled the diversity and noise in glucose data by constructing multiple decision trees and aggregating their predictions. This ensemble technique reduces overfitting and accommodates variations in glucose measurements and insulin regimens, enhancing classification robustness (26,44).

GBMs were employed for their ability to model complex relationships and sequentially refine predictions. By capturing subtle patterns in CGM data, GBMs improve accuracy and reliability in identifying the honeymoon phase, contributing to more personalized and effective treatment strategies (27-45).

The performance of these models was evaluated using metrics including accuracy, precision, recall, and F1-score, ensuring reliable detection of the honeymoon phase while minimizing false positives and negatives. These models collectively enhanced the classification of complex glucose patterns, supporting tailored insulin management for T1D patients (46).

Results

The honeymoon phase in T1D was identified through a comprehensive analysis of the patient's longitudinal glucose data, insulin dose adjustments, and ABS reports. This section details the process of identifying the honeymoon phase.

Glycemic Control and Insulin Adjustments

The GMI trends provided essential insights into glycemic control throughout the study. GMI estimates average glucose levels over time, helping assess the effectiveness of insulin therapy. As shown in Figure 5, GMI values initially indicated higher glucose levels (150 mg/dL in August 2022) due to the recent T1D diagnosis and insulin initiation. Over time, GMI values decreased consistently, reaching 125 mg/dL by May 2023, reflecting improved glycemic control and the onset of the honeymoon phase.

The most significant reduction in GMI occurred between May 2023 and August 2023, with values dropping to 112 mg/dL. This decline coincided with the identification of the honeymoon phase, marked by partial remission and decreased insulin needs. From August 2023 to February 2024, GMI values stabilized between 112-114 mg/dL, confirming the phase and enabling precise insulin dose adjustments based on CGM data. These results suggest that regular GMI monitoring supports effective identification and management of the honeymoon phase in T1D.

As detailed in Table 1, insulin dose adjustments reflected the fluctuations in insulin needs during the honeymoon phase, which is crucial for optimal management of T1D in this phase. In the early phase (August 2022 to February 2023), both average and minimum glucose levels gradually decreased, prompting reductions in insulin doses. This trend aligned with the onset of the honeymoon phase, where partial endogenous insulin production reduced the need for exogenous insulin. During the mid-phase (March 2023 to July 2023), further insulin reductions were made to address occasional hypoglycemic events, marking the peak of the honeymoon phase with the lowest insulin requirements. In the late phase (August 2023 to February 2024), glucose levels and insulin need stabilized, indicating the end of the honeymoon phase. These adjustments highlight the

importance of real-time monitoring to optimize insulin therapy and manage glucose levels effectively, minimizing the risks of hypoglycemia and hyperglycemia.

HbA1c Trends and Long-term Glycemic Control

Regular monitoring of HbA1c values provided critical insights into long-term glycemic control and its relationship with the honeymoon phase. As shown in Table 2, initial HbA1c levels of 6.9% in August 2022 decreased steadily to 5.8% by May 2023, marking the onset of the honeymoon phase. The most significant drop occurred by August 2023, with HbA1c reaching 5.3%, representing the peak of the honeymoon phase. From November 2023 to February 2024, HbA1c values stabilized between 5.6% and 5.9%, reflecting sustained glycemic control and successful management during this period. These findings demonstrate the honeymoon phase's potential to improve long-term glycemic control, which is essential for reducing the risk of diabetes-related complications.

By August 2023, HbA1c had dropped to 5.3%, aligning with the identification of the honeymoon phase—a period of partial remission and reduced insulin needs. This phase persisted, as reflected in HbA1c values of 5.9% in November 2023 and 5.6% in February 2024. These trends demonstrate the honeymoon phase's impact on improved glycemic control, and highlights the potential for optimizing diabetes management in the long term. Regular HbA1c monitoring provided essential insights for tailoring treatment strategies, ensuring better long-term outcomes.

The ML models were trained and validated using the collected datasets to identify the honeymoon phase, focusing on features such as glucose levels, insulin doses, glucose variability, hypoglycemic events, and HbA1c values. Their performance in detecting the honeymoon phase was evaluated based on predictive accuracy, sensitivity, specificity, and overall effectiveness, as summarized in Table 3.

Table 1. Insulin dose adjustments based on CGM

Patient ID	Date	Day average glucose (mg/dL)	Minimum glucose level (mg/dL)	Insulin dose adjustment	Notes
1	01.08.2022	150	120	Reduced	Slight decrease in insulin
1	01.11.2023	145	115	Reduced	Further decrease in insulin
1	01.02.2023	132	94	Reduced	Hypoglycemia detected
1	15.07.2023	92	57	Reduced	Hypoglycemia detected
1	20.07.2023	96	61	Reduced	Frequent hypoglycemia
1	25.07.2023	123	82	None	Normal glucose levels
1	01.08.2023	127	89	None	Normal glucose levels

Table 2. A1c trends and honeymoon phase correlation

Patient ID	Date	A1c (%)	Notes
1	01.08.2022	6.9	Initial report
1	01.11.2022	6.5	Slight decrease
1	01.02.2023	6.2	Continued improvement
1	01.05.2023	5.8	Stable control
1	01.08.2023	5.3	Honeymoon phase noted
1	01.11.2023	5.9	Honeymoon phase continued
1	01.02.2024	5.6	Honeymoon phase continued

Table 3. Performance metrics of machine learning models for identifying the honeymoon phase in type 1 diabetes

Model	Accuracy	Sensitivity	Specificity	Precision	Recall	F1 score
LSTM	88%	85%	90%	86%	85%	85%
Transformer	91%	89%	92%	90%	89%	89%
Random forest	87%	84%	89%	85%	84%	84%
Gradient boosting	89%	86%	91%	88%	86%	87%

LSTM: long short-term memory

In this study, the LSTM model, trained on daily glucose readings, insulin dosages, glucose variability, and hypoglycemic events, achieved an accuracy of 88%. It identified the honeymoon phase in 88% of test cases, with a sensitivity of 85% and specificity of 90%, demonstrating its effectiveness in detecting periods of insulin sensitivity associated with the honeymoon phase while minimizing false positives.

The transformer model, known for its ability to handle complex sequential data through self-attention mechanisms, achieved the highest accuracy of 91%. It had a sensitivity of 89% and a specificity of 92%, excelling in detecting subtle glucose fluctuations and transitions in insulin needs indicative of the honeymoon phase. Its capacity to process long-range dependencies contributed to its superior performance.

The random forest model achieved an accuracy of 87%, with a sensitivity of 84% and specificity of 89%. It effectively managed variability and noise in glucose data, distinguishing between different phases of diabetes management, making it a reliable tool for identifying the honeymoon phase.

The GBM model achieved an accuracy of 89%, with a sensitivity of 86% and a specificity of 91%. It excelled at capturing complex, non-linear relationships in CGM data, balancing sensitivity and specificity for accurate identification of the honeymoon phase.

The comparative analysis of the ML models revealed varying strengths in identifying the honeymoon phase in T1D, as shown in Figure 6. The transformer model led in performance highlighting its superior ability to capture complex patterns and long-range dependencies in glucose data. It outperformed the LSTM model, which achieved an accuracy of 88%, with a sensitivity of 85% and specificity of

90%. While the LSTM model effectively identified temporal dependencies, its slightly lower sensitivity suggests it may miss some true honeymoon phase cases, potentially leading to delayed insulin adjustments. The random forest achieved the next best performance and was strong when managing data variability but with slightly reduced sensitivity and accuracy compared to the transformer and LSTM models. These performance variations underscore the importance of model selection based on specific clinical needs, such as the need for high sensitivity in early honeymoon phase detection.

The GBM model was also effective and excelled in capturing non-linear relationships and subtle glucose trends. Overall, the transformer model's ability to handle complex data and long-range dependencies provided the most accurate and reliable identification of the honeymoon phase, while the other models offered valuable insights and robustness in different aspects of the analysis.

Discussion

This study demonstrated the potential of ML models, particularly the transformer and GBM, to accurately detect the honeymoon phase in T1D patients. The models achieved high accuracy, with the transformer model reaching 91%, suggesting that ML can effectively identify periods of reduced insulin requirements and improved glycemic control.

Our findings align with previous research highlighting the utility of ML in diabetes management, particularly in predicting glucose trends and optimizing insulin therapy. However, our study uniquely focused on the honeymoon phase, a critical transitional period that has been underexplored in prior ML studies (21,22,23,24,25,26,27,28,29). While other studies have

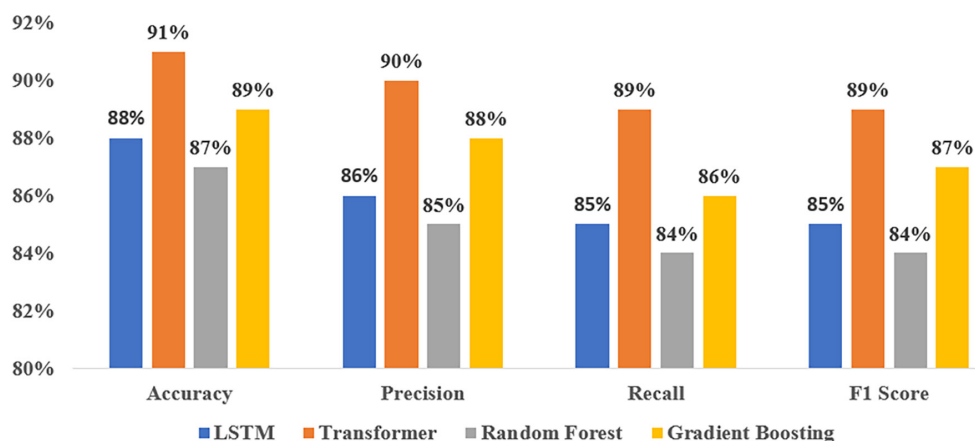


Figure 6. Performance metrics of machine learning models

LSTM: long short-term memory

explored glucose prediction and long-term management, our study is the first to investigate the dynamic insulin needs during the honeymoon phase and how ML can facilitate its early detection (42,43,44,45).

While the models' overall performance was promising, discrepancies were observed when applied to pediatric patients. These discrepancies may be attributed to age-related variations in insulin sensitivity, growth patterns, and puberty, which were not fully accounted for in the models. This underlines the need for further research to refine the models by incorporating pediatric-specific factors.

Clinical Implications

The high accuracy of these ML models suggests their potential for integration into clinical decision support systems. Early identification of the honeymoon phase allows clinicians to adjust insulin therapy more effectively, optimizing glycemic control and reducing the risk of hypoglycemia and hyperglycemia. By incorporating real-time data from CGM, the models can offer personalized recommendations for insulin dose adjustments, improving overall diabetes management.

Limitations and Future Directions

Despite the promising results, the generalizability of the models to pediatric populations remains a limitation. The current models were trained on adult data, and further studies should focus on validating these models in pediatric populations, incorporating factors such as age, pubertal insulin resistance, and growth patterns. Future research should also explore the integration of genetic factors, lifestyle variables, and more granular patient-specific data to improve the models' predictive accuracy.

Recommendations

The insights gained from the ML models offer valuable guidance for personalizing insulin management during the honeymoon phase of T1D. By accurately identifying this phase, clinicians can tailor insulin therapy to better align with the patient's changing insulin needs, optimizing glycemic control and reducing the risk of hypoglycemia and hyperglycemia.

This study highlights the importance of CGM and other key metrics in recognizing the honeymoon phase. Implementing a structured monitoring protocol that leverages these findings can lead to more effective tracking of glucose levels, insulin dosages, and fluctuations, ensuring timely adjustments to treatment plans during this transitional period.

It is important to note that pediatric patients may exhibit different insulin sensitivity and glucose patterns than adults. Therefore, further research is needed to validate the applicability of these models in pediatric diabetology. Age-related insulin sensitivity, growth, and pubertal changes may affect the performance of the models in children.

Validation across larger and more diverse patient cohorts is essential to ensure the robustness and generalizability of the findings. Expanding the dataset will provide clearer insights into how well the models perform in varied clinical settings and demographics. In addition, refining the ML models by incorporating patient-specific factors, genetic information, and lifestyle variables will enhance their ability to handle complex data patterns. Continuous improvements in these models will contribute to more accurate predictions, further personalizing care, and ultimately leading to better management of T1D during the honeymoon phase.

Conclusion

This study presents a robust ML-driven approach for identifying the honeymoon phase in T1D, using a comprehensive dataset that included CGM data, GMI reports, HbA1c values, and patient medical history. The implementation of LSTM networks, transformer models, random forest, and GBM has shown potential for accurately detecting this critical phase, with model accuracies ranging from 87% to 91%. The ML models effectively identified the honeymoon phase, enabling more precise insulin management and improved glucose control. This approach may enhance the optimization of insulin therapy and reduce the risk of adverse glycemic events, such as hypoglycemia. The successful application of these models underscores their potential for integration into clinical practice, offering a valuable tool for personalized diabetes management.

Future research should focus on evaluating the long-term impact of these ML-driven insulin management strategies on patient outcomes. Specifically, exploring how such models influence the duration of the honeymoon phase, overall glycemic control, and the prevention of diabetes-related complications could provide valuable insights into optimizing care for T1D patients. Moreover, studies exploring the real-time adaptation of these models to changing patient conditions would be key to enhancing clinical decision-making. Finally, future work could aim to integrate these models into digital health platforms, enabling seamless use in clinical settings and expanding access to personalized care for a wider patient population.

Ethics

Ethics Committee Approval: The study was approved by the Narasaraopeta Engineering College: Narasaraopeta of Institutional Review Board (IEC ref. no: 01/2024, date: 28.08.2024).

Informed Consent: Informed consent was acquired from the patient for the use of their data in this study.

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