Original Paper

In-Silico Works Using an Improved Hovorka Equations Model and Clinical Works on the Control of Blood Glucose Levels in People With Type 1 Diabetes: Comparison Study

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Abstract

Background: People with type 1 diabetes (T1D) depend on external insulin to regulate their blood glucose level (BGL) within the normoglycemic range between 4.0 to 7.0 mmol/L. Patients with T1D routinely conduct self-monitoring of blood glucose through finger pricks before insulin injections. An artificial pancreas is an innovative device that mimics the function of a healthy pancreas. Despite its recent advancement, the control algorithms used in an artificial pancreas are still lagging in delivering the proper insulin dosage to patients with T1D. Previous researchers attempted to improve the interrelation between parameters and variables in the original Hovorka equations model, later known as the improved Hovorka equations model; however, the improved equations model has not been tested in terms of its usability to regulate and control the BGL in a safe range for 2 or more people with T1D.

Objective: This study aimed to simulate the improved Hovorka equations model using actual patients' data via MATLAB programming coupled with enhanced model-based predicted control and determine the optimum bolus insulin. The study then compares the performance results obtained from in-silico and clinical works.

Methods: Data from 3 patients were collected from clinic 1—Clinical Training Centre, Universiti Teknologi MARA Hospital, Sungai Buloh, Selangor—upon getting approval from the Universiti Teknologi MARA Ethics Committee. The inclusion criteria for participation were, namely having T1D, age 11-14 years, and highly dependent on insulin injection with four or more finger pricks or self-monitoring of blood glucose for BGL measurements per day. The patients with T1D typically received meals three times per day: breakfast, lunch, and dinner. A closed-loop algorithm (enhanced model-based predicted control) was used for the in-silico test, whereas an open-loop therapy was used for the clinical validation. As for the data analysis of patients, *P* values from a multiple linear regression were used to model the relationship between meal, insulin, and BGL.

Results: The optimum bolus insulins for patient 1 were 83.33, 33.33, and 16.67 mU/min; for patient 2 were 66.67, 50.01, and 33.33 mU/min; and for patient 3 were 100.02, 83.33, and 66.67 mU/min for breakfast, lunch, and dinner, respectively. As for the in-silico works, the percentages of time that the BGL was on target for patients 1, 2, and 3 were 79.59%, 87.76%, and 71.43%,

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respectively, as compared to the clinical works with <50%. A small *P* value (*P*<.001) indicated that the variables were significant. However, when compared to the BGL profile, both profiles were not comparable in simulating the BGL for patients with T1D.

Conclusions: The in-silico work was not comparable to the clinical work in simulating the BGL for patients with T1D due to the different methodologies used and the insufficient information that was reported to reproduce the calculation of the optimal bolus insulin.

(JMIRx Bio 2024;2:e43662) doi: 10.2196/43662

KEYWORDS

blood glucose level; closed-loop system; Hovorka model; in-silico work; meal disturbance; type 1 diabetes mellitus

Introduction

Diabetes is a chronic disease that is characterized by high blood glucose levels (BGLs). It occurs when beta cells in the pancreas produce insufficient insulin or cells are unable to use insulin effectively. Insulin is crucial in blood glucose regulations by promoting glucose uptake, consequently lowering the BGL [1], which should be regulated within the normoglycemic range between 4.0 and 7.0 mmol/L [2]. Maintaining BGLs in a safe range can help prevent long-term complications related to hyperglycemia (high BGL) and hypoglycemia (low BGL). A lack of insulin production in patients with type 1 diabetes (T1D) thus disrupts blood glucose regulation. T1D commonly occurs in children and adolescents. The incidence of T1D is more prevalent in Northern Europe than in the rest of the world. The International Diabetes Federation reported 977 cases of T1D in Malaysian children ages 0 to 19 years in 2019 [3]. People with T1D must monitor their BGL via finger pricks and either perform self-monitoring of blood glucose (SMBG) or take multiple daily injections (MDI) of insulin to regulate their BGL.

The current practice for blood glucose management is invasive, which causes distress to patients. Thus, the introduction of an artificial pancreas device (APD), also known as a closed-loop system, has improved the quality of life for people with T1D for the last few decades. An APD has the potential to impact millions of people by helping regulate BGLs. Additionally, being able to estimate this (even a low-end estimate) with modeling work reduces material costs, time, and patient risk. Despite the recent advancements in APDs, the control algorithms used are still lagging in delivering the proper insulin dosage to people with T1D. Previous works had modified some equations in the subsections of the Hovorka model [4], which is also known as the improved Hovorka equations model, in regulating the BGL within a normoglycemic range (4.0-7.0 mmol/L) [5,6]. However, the improved Hovorka equations model has not yet been tested in terms of its usability to regulate and control the BGLs in a safe range for two or more people with T1D. This study aims to simulate the improved Hovorka equations model using actual patients' data via MATLAB programming (in-silico works) coupled with enhanced model-based predicted control (eMPC) and compare its performances with clinical works. This study is a continuation of preliminary in-silico works from the previous studies [7-9] carried out on a single patient with T1D using the improved Hovorka equations model.

Methods

Ethics Approval on Data Collection for Clinical Works

Ethical approval for this study (REC/435/19) was granted by the Universiti Teknologi MARA (UiTM) Ethics Committee before data collection commenced (reference letter 600-TNCPI (5/1/6) dated 29 October 2019). The data collection and patients' information required in this study were obtained from clinic 1—Clinical Training Centre, UiTM Medical Specialist Centre, UiTM Hospital, Sungai Buloh, Selangor. Information sheets were given, and formal consent for participation from the parents or legal guardians of patients with T1D was obtained since the patients were all younger than 18 years. During the appointment, parents or guardians of participants (ie, patients with T1D) were allowed to ask questions before signing the consent form. The participants could withdraw from the study at any time without penalty. Participants' details, such as names or other personal identifiers, remain confidential in the data used by the researchers.

A total of 3 patients with T1D were recruited following informed consent. The inclusion criteria of patients were patients with T1D; age 11-14 years; and highly dependent on insulin injection with four or more finger pricks or SMBG for BGL measurements per day, MDI of insulin, and a well-documented bolus insulin requirement. The exclusion criteria were patients with T1D with evidence of hypoglycemia unawareness; known or suspected allergy to insulin; or established neuropathy, nephropathy, and retinopathy. Patients with T1D attended the clinic every 3 months and required blood taking as routine follow-up care. The amount of blood taken by the pediatrician was 5 mL each for fasting glucose and fasting insulin and was taken once. The additional data required included the patient's name, age, gender, race, body weight, BMI, type and amounts of meals consumed (specifically carbohydrates), meal time and duration, T1D history (years diagnosed with T1D), fasting plasma glucose level, fasting plasma insulin level, bolus insulin administered, and other relevant information. The patients with T1D typically received meals three times per day: breakfast, lunch, and dinner. The patients' data were termed clinical data (clinical work) throughout the study. Table 1 summarizes the demographic profiles of the patients with T1D, including gender, age, and body weight.

Table 2 provides a 24-hour meal summary for all patients that includes meal time and duration, and amounts of meals consumed (in grams of carbohydrates).

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Table 1. Demographic profiles of patients with type 1 diabetes.

Patient	Gender	Age (years) in 2020	Body weight (kg)
1	Male	13	27.0
2	Female	11	26.3
3	Male	14	49.9

Table 2. Meal summaries for patients 1-3 over 24 hours.

Meal	Mealtime (hours passed since simulation started at 5 AM)	Meal duration (min)	Total carbohydrates (g)
Patient 1			
Breakfast	7:30 AM (2.5 h)	30	36
Lunch	1:30 PM (8.5 h)	30	36
Dinner	7 PM (14 h)	30	47
Patient 2			
Breakfast	6 AM (1 h)	10	30
Lunch	1 PM (8 h)	20	41
Dinner	8 PM (15 h)	20	49
Patient 3			
Breakfast	8:15 AM (3.5 h)	30	67
Lunch	3 PM (10 h)	10	124
Dinner	8:45 PM (15.5 h)	15	47

Mathematical Model for In-Silico Works

The improved Hovorka equations [5,7] based on the Hovorka model [4] are specifically designed for people with T1D. The diagram of the improved Hovorka equations model is illustrated in Figure 1 [7]. The model has two inputs: meal disturbances and bolus insulin. It comprises three subsystems: the glucose subsystem, insulin subsystem, and insulin action subsystem. Equations 1 and 2 are used for the glucose subsystem:

$$\frac{dQ_1(t)}{dt} = EGP_0 + U_G + 0.01Q_2 + [x_1k_{w1} + x_2k_{w2} + x_3k_{w3}] - F_RQ_1 - \left[\frac{F_{01}{}^C}{V_G G(t)}\right]Q_1 - 0.002Q_1 \quad (1)$$

$$\frac{dQ_2(t)}{dt} = [k_{w11}x_1(t) + k_{w22}x_2(t) + k_{w33}x_3(t)] + EGP_0[k_{w1}x_1(t) + k_{w2}x_2(t) + k_{w3}x_3(t)] - k_{12}Q_2 \quad (2)$$

$$F_{01}{}^C = \begin{cases} F_{01} & \text{if } G \geq 4.5 \text{ mmolL}^{-1} \\ F_{01}G/4.5 & \text{otherwise} \end{cases} \quad (3)$$

$$F_R = \begin{cases} 0.003(G-9)V_G & \text{if } G \geq 9 \text{ mmolL}^{-1} \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

where Q_1 (mmol) is the mass of glucose in an accessible compartment; Q_2 (mmol) is the mass of glucose in a nonaccessible compartment; k_{w1}, k_{w11}, k_{w2}, k_{w22}, k_{w3}, and k_{w33} (min^{-1}) are activation rates; k_{12} (min^{-1}) is the transfer rate; EGP_0 is the endogenous glucose production (EGP) extrapolated to zero insulin concentration; V_G (L/kg) is the glucose distribution volume; G (mmol/L) is the glucose concentration; x_1, x_2, and x_3 are the effects of insulin on glucose transport and distribution, glucose disposal, and EGP, respectively; $F_{01}{}^C$ (mmol min^{-1} kg^{-1}) is the total non–insulin-dependent glucose flux; and F_R (mmol/min) is the renal glucose clearance.

When a meal is consumed, the carbohydrate content will be broken down into glucose before being converted into energy, thus increasing the BGL. Equation 5 was used for observing the effect of meal disturbances on BGLs.

$$U_G = \frac{D_G A_G t e^{-t/t_{max,G}}}{t_{max,G}{}^2} \quad (5)$$

where D_G is the amount of carbohydrates digested (mmol), A_G is the carbohydrate availability, and $t_{max,G}$ is the time-to-maximum of carbohydrate absorption (min).

Equations 6-8 show the insulin subsystem. Insulin is administered subcutaneously. This method is less invasive than the intravenous method, in which insulin is injected directly into the bloodstream.

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{max,I}} \quad (6)$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \quad (7)$$

$$\frac{dI(t)}{dt} = \frac{U_I(t)}{V_I} - k_eI(t) - [k_{w1}x_1(t) + k_{w2}x_2(t) + k_{w3}x_3(t)] \quad (8)$$

The insulin absorption rate in the bloodstream is given in equation 9.

$$U_I = \frac{S_2(t)}{t_{max,I}} \quad (9)$$

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where S_1 and S_2 (mU) are the insulin sensitivity in accessible and nonaccessible compartments, respectively; u(t) (mU/min) is the insulin infusion rate; $t_{max,I}$ (min) is the time-to-maximum of insulin absorption; U_I (mU/min) is the insulin absorption rate; V_I (L/kg) is the insulin distribution volume; and k_e (min^{-1}) is the fractional elimination rate.

The insulin action subsystem is shown in equations 10-12. The insulin-glucose interaction can be observed in this subsystem.

$$\left[\frac{dx_1}{dt}\right] = k_{a1}x_1(t) + k_{w1}I(t) + k_{w11}I(t) \quad \textbf{(10)}$$

$$\left[\frac{dx_2}{dt}\right] = k_{a2}x_2(t) + k_{w2}I(t) + k_{w22}I(t) \quad \textbf{(11)}$$

$$\left[\frac{dx_3}{dt}\right] = k_{a3}x_3(t) + k_{w3}I(t) + k_{w33}I(t) \quad \textbf{(12)}$$

The constants and parameters involved in the equations are shown in Tables 3 and 4, respectively.

Figure 1. Schematic diagram of the improved Hovorka equations model.

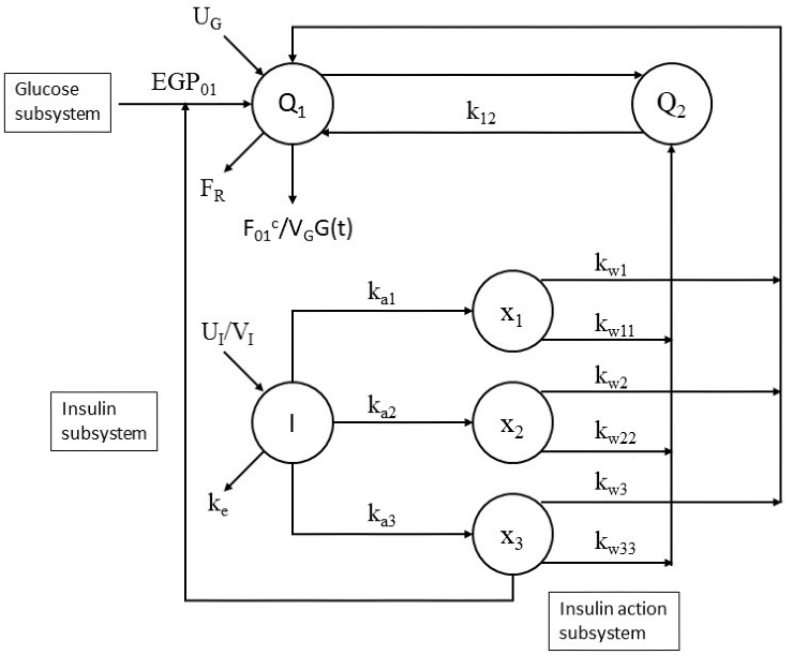


Table 3. Constant values of the improved Hovorka equations model [7,10].

Symbol	Constant	Value and unit
k_{12}	Transfer rate from nonaccessible to accessible compartment	0.066 min^{-1}
k_{a1}	Deactivation rate of glucose	0.006 min^{-1}
k_{a2}	Deactivation rate of glucose	0.06 min^{-1}
k_{a3}	Deactivation rate of glucose	0.03 min^{-1}
k_{w1}	Activation rate of glucose	50.1 min^{-1}
k_{w11}	Activation rate of glucose	–10 min^{-1}
k_{w2}	Activation rate of glucose	50.1 min^{-1}
k_{w22}	Activation rate of glucose	–0.01 min^{-1}
k_{w3}	Activation rate of glucose	50.1 min^{-1}
k_{w33}	Activation rate of glucose	–0.01 min^{-1}
k_e	Insulin elimination from plasma	0.138 min^{-1}
V_I	Insulin distribution volume	0.12 Lkg^{-1}
V_G	Glucose distribution volume	0.16 Lkg^{-1}
A_G	Carbohydrate bioavailability	0.8 (unitless)
$t_{max,G}$	Time-to-maximum of carbohydrate absorption	40 min

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Table 4. Parameter values of the improved Hovorka equations model [7,10].

Symbol	Parameter	Value and unit
EGP_0	Endogenous glucose production extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}
F_{01}	Non–insulin-dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}
$t_{max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min

Meals and Insulin Requirement

The in-silico work on the meal disturbances was based on the patients' daily meal intake. Table 5 shows an example of the amount of daily meal intake, specifically carbohydrates, suggested for 13-year-old male patients. The suggested meal intake is based on the total daily calorie requirement, which varies according to age and gender (refer to Table 6). It consists of breakfast, lunch, and dinner, which are adopted into the in-silico work using the improved Hovorka equations model. Generally, 50% of the calorie intake comes from carbohydrates [11].

Table 5. Example of amount of carbohydrate (CHO) intake for a 13-year-old male patient.[a]

Meal	Time	CHO (g)	CHO (mol)	CHO (mmol)
Breakfast	6 AM	60	2.068	2068
Lunch	12 PM	90	3.102	3102
Dinner	7 PM	90	3.102	3102
Total	__[b]	240	8.272	8272

[a]Source: patient with type 1 diabetes at clinic 1—Clinical Training Centre, Universiti Teknologi MARA Medical Specialist Centre, Sungai Buloh.
[b]Not applicable.

Table 6. Daily energy (calorie) requirement by weight for children and adolescents [12].

Age	Energy (kcal/kg/day)
0-6 months	≥108
7-12 months	≥98
1-3 years	102
4-6 years	90
7-10 years	70
11-14 years	Male: 55; female: 47
15-18 years	Male: 45; female: 40

The calculations of carbohydrate intake and insulin requirement can be further explained in the following example.

For a 13-year-old male patient with T1D and a body weight of 36 kg, the daily energy (calorie) requirement by weight based on Table 6 for male patients ages 11-14 years can be calculated as:

Daily energy (calorie) requirement by weight = 55 kcal/kg/day

So, 55 kcal/kg/day × 36 kg = 1980 kcal/day

50% of calories intake comes from CHO:

Therefore, $\frac{1980}{2} = 990$ kcal/day CHO

$\therefore$ 4 kcal = 1g CHO (unit conversion)

$\frac{990}{4} = 247.5$g CHO ± 240g CHO*

Referring to the previous calculation, a patient with a body weight of 36 kg required approximately 240 grams of carbohydrates. The bolus (exogenous) insulin required per day can be calculated based on this value. If excess insulin is infused, patients may experience hypoglycemia (low BGL) [13]. Generally, 1 unit of rapid-acting insulin can cover 10-15 grams of carbohydrates [14]. However, this range can vary from 6 to 30 grams depending on the individual's sensitivity to insulin, and insulin sensitivity for an individual may vary for a different period [14]. The total daily dose (TDD) of insulin can be calculated based on the insulin-to-carbohydrate ratio used, which is 1:15, as shown in equation 13.

TDD = Total amount of CHO intake **(13)**

÷ 15 g of CHO disposed of by 1 unit of insulin

Therefore,

TDD = 240 g CHO ÷ 15 g of CHO disposed of by 1 unit of insulin

TDD = 16 units of rapid-acting insulin

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The TDD of insulin required to cover 240 grams of carbohydrate intake is 16 units based on the above calculation. In addition, a few parameters related to the patient's body weight are being considered, including V_I, V_G, EGP_0, and F_{01} as seen in Tables 3 and 4. Another calculation example is shown below.

For patient 1, with a body weight of 27 kg, the following parameter values were used:

$$V_I = 0.12\ \text{L/kg} \times 27\ \text{kg} = 3.24\ \text{L}$$

$$V_G = 0.16\ \text{L/kg} \times 27\ \text{kg} = 4.32\ \text{L}$$

$$EGP_0 = 0.0161\ \frac{\text{mmol}}{\text{min}}/\text{kg} \times 27\ \text{kg} = 0.4347\ \frac{\text{mmol}}{\text{min}}$$

$$F_{01} = 0.0097\ \frac{\text{mmol}}{\text{min}}/\text{kg} \times 27\ \text{kg} = 0.2619\ \frac{\text{mmol}}{\text{min}}$$

The same equations were applied to patients 2 and 3 with a body weight of 26.3 kg and 49.9 kg, respectively.

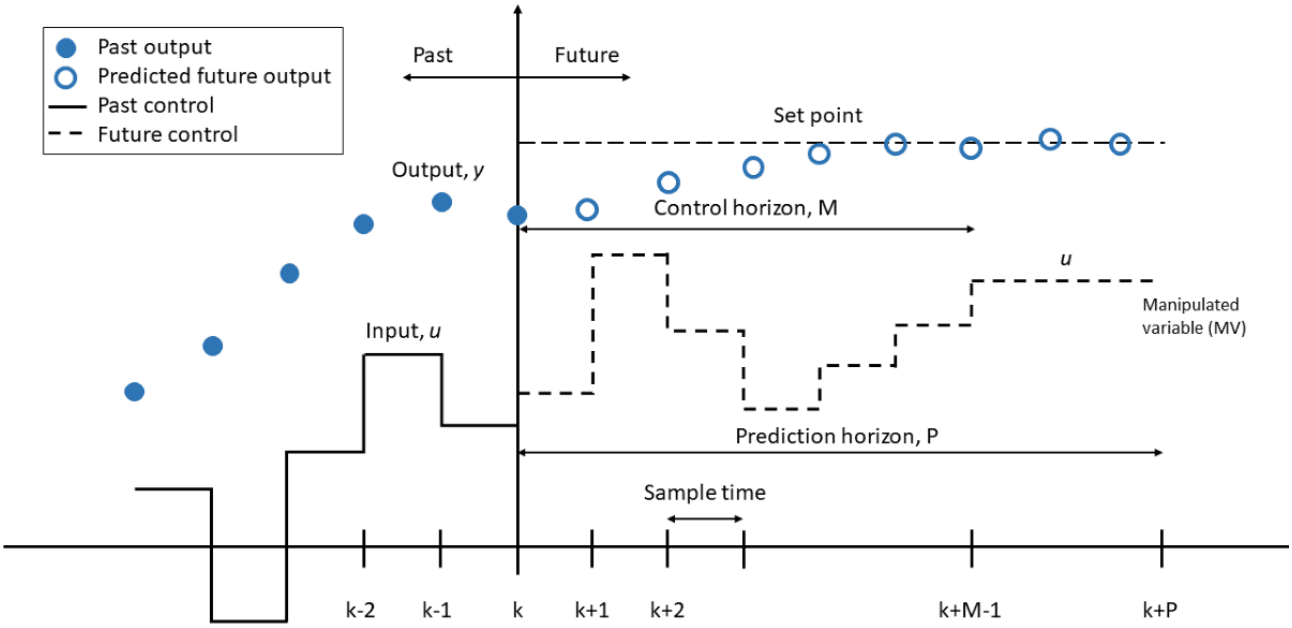
Consequently, all simulated data via in-silico works for the 3 patients with T1D were collected and plotted to produce profiles of BGL versus time for each patient. Upon completion of data collection and construction of sufficient BGL versus time profiles for both clinical and in-silico works, these two results were analyzed and compared for any similarities or differences.

Enhanced Model Predictive Control

The eMPC used in this study is an extension of MPC, which uses a mathematical model of a system to predict its future behavior over a certain period. The prediction was then used to determine the optimal control to achieve the desired objective. To control the BGL in patients with T1D, eMPC was integrated into the improved Hovorka equations model meant for patients with T1D to predict BGLs in response to different insulin dosages and other inputs, thus optimizing the insulin dosing in real time. The model considers factors that influence the outcome of the BGL profile such as the current BGL, amount of carbohydrates consumed, and time and duration of meals and insulin. The eMPC algorithm uses these predictions to calculate the optimal insulin dosage so patients can achieve a desired BGL target range.

Figure 2 [15] illustrates the general concept of MPC. The prediction horizon, P, would be the outcome of the BGL based on the previous inputs, u, insulin infusion rate, and meal disturbances. Constraints were imposed such that the target range for BGL, G(t), was within the normoglycemic range of 4.0 to 7.0 mmol/L. The set point is set to 5 mmol/L. The insulin infusion rate, u(t), was between 0 to 35 U/hr based on the current insulin pump specification [16]. The control algorithm predicted the BGL output to be closer to the set point. The eMPC is prone to deliver more insulin to counter the hyperglycemia event. The controller is also able to shut down insulin pump infusion to minimize the occurrence of hypoglycemia.

Figure 2. General concept of model predictive control.



Initial values for S_1, S_2, x_1, x_2, and x_3 were set at zero since the insulin had not been injected into the patient's body, and the insulin being administered, which caused glucose transport/distribution, glucose disposal, and EGP, had not yet occurred. The bolus insulin for each meal was obtained on a trial-and-error basis to minimize the BGL to the normal range while avoiding hypoglycemia (<4.0 mmol/L). Since the blood glucose ($t_{max,G}$=40 min) reached the bloodstream sooner than the insulin ($t_{max,I}$=55 min), the bolus insulin was administered 30 minutes before a meal due to the time lag for insulin to penetrate the skin and take effect. Figures 3 and 4 show a part of the control system algorithm for glucose, G(i), and bolus insulin, u(i). When the BGL falls below the range, the insulin pump stops delivering insulin. In contrast, the insulin is continuously delivered when the BGL is above 4.0 mmol/L.

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Figure 3. Part of the control system algorithm: glucose.

```
% Glucose
G(i) = Q1(i)/Vg;
if G(i)>=4.5
    Fc_01 = F01;
else
    Fc_01 = F01*G(i)/4.5;
end
if G(i)>=9
    Fr(i) = 0.003*(G(i)-9)*Vg;
else
    Fr(i) = 0;
end
```

Figure 4. Part of the control system algorithm: bolus insulin.

```
% Bolus insulin
if t(i)>=120 && t(i)<=121
     u(i) = 83.33;
elseif t(i)>=480 && t(i)<=481
    u(i) = 33.33;
elseif t(i)>=810 && t(i)<=811
    u(i) = 16.67;
else
    if G(i) <= 4
        u(i) = 0;
    else
        u(i) = u(1); %u(1)
    end
end
```

The in-silico work of BGLs against time was conducted, and the results were compared to the clinical work. The comparison focused on assessing how well the in-silico model performed in controlling BGLs. This evaluation helps determine the accuracy and effectiveness of the in-silico model in mimicking real-world BGL dynamics.

Data Analysis of Patients

Previously, the BGL profiles for both works were created. The BGL profiles in the clinical work were done manually by inserting related data and plotting the BGL profiles using Microsoft Excel 2016. Conversely, the BGL profiles in the silico work were generated using MATLAB R2015a (MathWorks). From there, the pattern of blood glucose profiles was observed and identified, such as the time of day when BGLs tend to be the highest or lowest, the frequency of hypoglycemic and hyperglycemic events, and the variability of BGLs. The BGL profiles were used to evaluate the patients' glycemic control over the selected time frame by calculating the average BGL and the percentage of time spent in different glycemic ranges, such as hypoglycemia, normoglycemia, and hyperglycemia, among other things.

Thus, Microsoft Excel 2016 was used to facilitate the data analysis work. Data such as the amounts of meals (grams of carbohydrates), mealtime and duration, and amount of plasma insulin and plasma glucose were used. A regression analysis was selected, which is a statistical method generally used to analyze the relationship between two or more variables. A multiple linear regression (MLR) is a type of regression analysis that is done to analyze the relationship between two or more independent variables and a dependent variable. In this case, the two independent variables were the amounts of meals consumed and insulin administered, while the dependent variable was the predicted BGL. The following steps were performed for the MLR.

The first step was to enter the data into the Excel spreadsheet with one column for the dependent variable and one or more columns for the independent variables. From the data tab, data analysis containing various analysis tools was selected. The regression analysis was chosen where the selected input of the y range was the BGL outcome and the inputs of the x range were meals consumed and insulin administered. A new worksheet tab appeared, giving the summary output of the regression statistics and other relevant information. The probability value (P value) and coefficient of determination (R^2) are important statistical measures used in regression analysis. The P value was used to test the research hypothesis (whether to reject or support the null hypothesis). A small P value (P<.05) indicates that the relationship between the variables is significant and the null hypothesis is rejected. R^2 measures how much the independent variables explain the variation in the dependent variable. A high R^2 value indicates a better fit of the model to the data.

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Results

Simulation of Meal Disturbances

The amount of food consumed during a meal, especially carbohydrates, has been shown to impact the meal rate directly. When people consume larger meals, they tend to eat at a slower rate, taking more time to chew and swallow their food. This is likely because larger meals require more time and effort to eat, resulting in a reduced meal rate as opposed to smaller meals [17]. Besides, the meal duration also has an impact on the meal rate. A shorter meal duration is associated with a faster meal rate than a longer one [18]. The calculation of the meal rate was referred to in [19]. The meal rates were determined by dividing the total carbohydrates (in grams of carbohydrates) by meal duration (in minutes).

The meal rate calculation is as follows:

$$\text{Meal rate (g CHO/min)} = \frac{\text{Total of carbohydrates (g CHO)}}{\text{Meal duration (min)}} \quad (14)$$

Therefore, take patient 1 as an example:

$$\text{Meal rate (g CHO/min)} = \frac{36\ \text{g CHO}}{30\ \text{min}}$$

$$\text{Meal rate (g CHO/min)} = 1.2\ \text{g}\frac{\text{CHO}}{\text{min}}$$

The same thing applies to other meals for all patients and is summarized in Table 7. All patients consumed each meal at a different duration between 10 to 30 minutes. The simulation started at 5 AM, and patients had their first meal at least 1 hour after, that is, at 6 AM and onward.

Table 7. Meal rates for patients 1-3.

Meal	Meal duration (min)	Carbohydrates (g)	Meal rate (g/min)
Patient 1			
Breakfast	30	36	1.20
Lunch	30	36	1.20
Dinner	30	47	1.57
Patient 2			
Breakfast	10	30	3.00
Lunch	20	41	2.05
Dinner	20	49	2.45
Patient 3			
Breakfast	30	67	2.24
Lunch	10	124	12.40
Dinner	15	47	3.00

Based on the table, patient 1 has a fixed meal duration of 30 minutes for each meal. Although patient 1 consumed a smaller meal amount, patient 1 had the lowest meal rate due to longer meal duration. Patient 2 also had a fixed meal duration of 20 minutes, except for breakfast, which took only 10 minutes. The meal rate for patient 2 was comparatively similar to patient 1 since the meal amount and duration were quite close to one another. Patient 3 did not have a fixed meal duration, varying between 10 to 30 minutes for each meal. Patient 3 also consumed the largest meal in a shorter duration during lunch, thus having the largest meal rate.

The Effect of Meal Disturbances on BGL Profiles Between Clinical and In-Silico Works for Patient 1

In this section, in-silico works of BGLs with three meals were performed for patient 1. This BGL profile between clinical and in-silico works was compared and analyzed. The BGL profile was simulated using the improved Hovorka equations model. The patients' premeal and postmeal BGLs in clinical works are shown in Table 8.

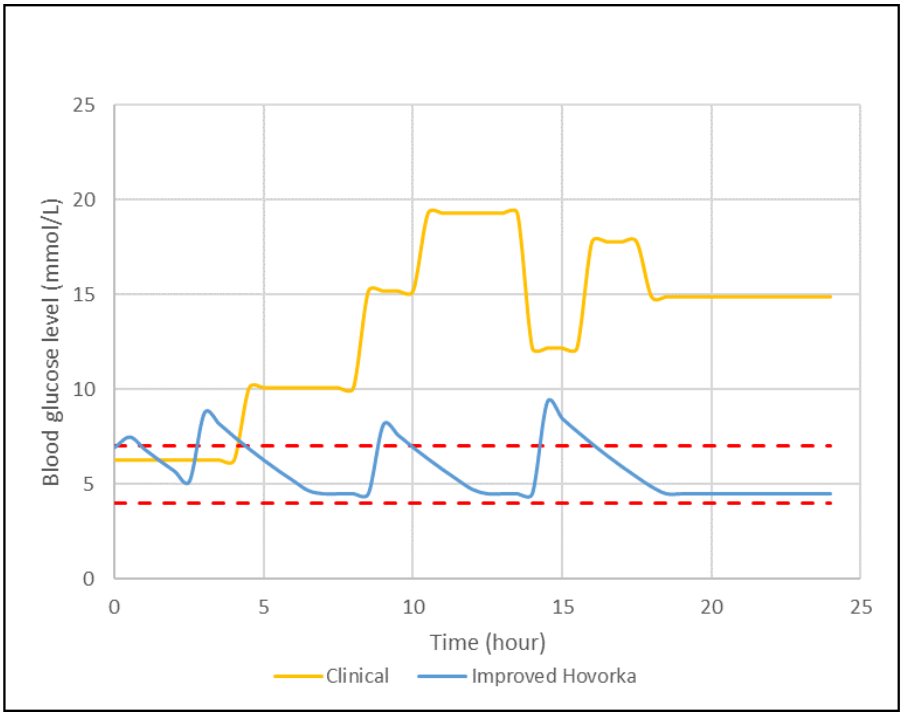
Table 8. Blood glucose reading for patient 1 in 24 hours.

Meal	Blood glucose level (mmol/L)	
	Premeal	Postmeal
Breakfast	6.3	10.1
Lunch	15.2	19.3
Dinner	12.2	17.8

Figure 5 shows the BGL profile in a day for patient 1 for both clinical and in-silico works. Each peak shown in the graphs is the BGL fluctuation during breakfast, lunch, and dinner. The red line represents the normoglycemic range of 4.0 to 7.0 mmol/L. The blue and orange lines represent BGL profiles for in-silico and clinical works, respectively.

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Figure 5. Blood glucose profile in a day between clinical and in-silico works for patient 1.



As shown in Figure 5, during the fasting stage (or no meal disturbances), patient 1 in the clinical work recorded a BGL value of 6.3 mmol/L; whereas in the in-silico work, it was 6.9 mmol/L. Initially, the BGL trends were similar during the first 3 hours. The BGL then fluctuated during breakfast, lunch, and dinner. However, the BGL in the in-silico work managed to achieve the normoglycemic range a few hours past the meal, as opposed to the patient in the clinical work who experienced hyperglycemia most of the day and only achieved normoglycemia for 18.37% of the time (ie, during breakfast). The average BGLs for the patient in the clinical and in-silico works were 13.21 mmol/L and 5.74 mmol/L, respectively. The highest BGL recorded in the clinical trials was 19.30 mmol/L post lunch. In the in-silico work, the highest BGL recorded was 9.31 mmol/L post dinner and normoglycemia was achieved 79.59% of the time.

The Effect of Meal Disturbances on BGL Profiles Between Clinical and In-Silico Works for Patient 2

In this section, in-silico works of BGL with three meals were performed for patient 2 and then compared and analyzed with the clinical works. The patient's premeal and postmeal BGLs in the clinical works are shown in Table 9.

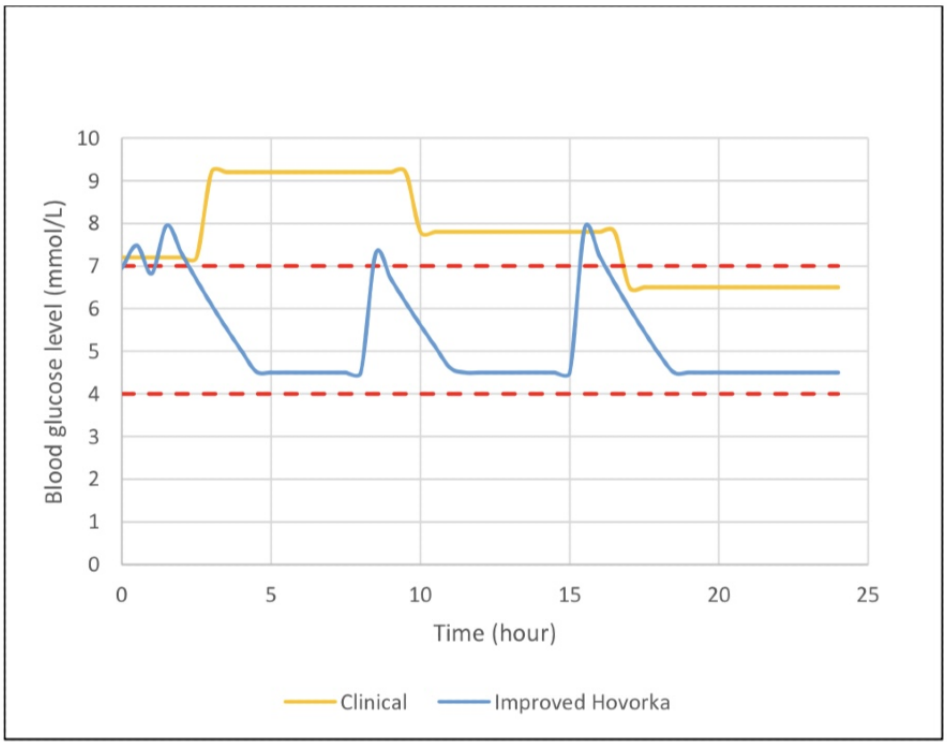
Table 9. Blood glucose reading for patient 2 for 24 hours.

Meal	Blood glucose level (mmol/L)	
	Premeal	Postmeal
Breakfast	7.2	9.2
Lunch	9.2	7.8
Dinner	7.8	6.5

Figure 6 shows the BGL profile in a day for patient 2 for both clinical and in-silico works. As shown in the figure, the BGLs recorded for clinical and in-silico works at the fasting stage were 7.2 mmol/L and 6.9 mmol/L, respectively. It can be observed that the BGL profiles are quite similar in both works, especially post dinner. The average BGLs recorded for the patient in the clinical and in-silico works were 7.73 mmol/L and 5.29 mmol/L, respectively. The highest BGL recorded for patient 2 in the clinical work was 9.2 mmol/L, while in the in-silico work, it was 7.9 mmol/L. Patient 2 in the in-silico work stayed in the normoglycemic range for 87.76% of the time compared to the clinical work, which was 30.61% of the time. Even though patient 2 in the clinical work was unable to attain a longer duration of normoglycaemia, the BGL remained relatively low and closer to the normoglycemic range throughout the day.

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Figure 6. Blood glucose profile in a day between clinical and in-silico works for patient 2.



The Effect of Meal Disturbances on BGL Profiles Between Clinical and In-Silico Works for Patient 3

The in-silico works of BGL versus time with three meals were then compared and analyzed with the clinical works of patient 3. The patient's premeal and postmeal BGL in the clinical works are shown in Table 10.

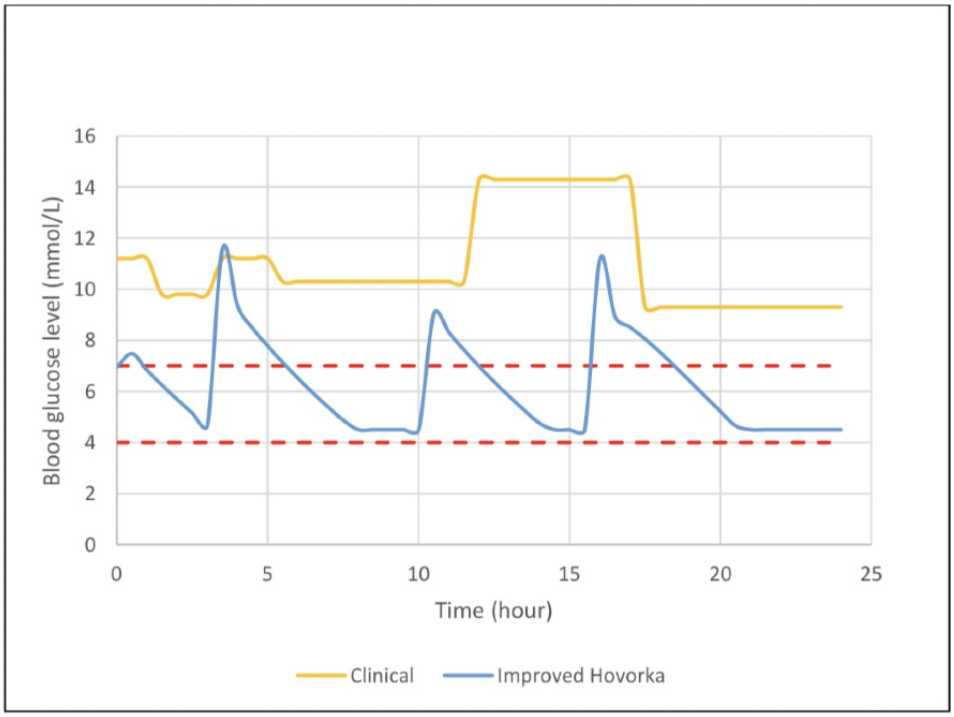
Table 10. Blood glucose reading for patient 3 for 24 hours.

Meal	Blood glucose level (mmol/L)	
	Premeal	Postmeal
Breakfast	11.2	10.3
Lunch	10.3	14.3
Dinner	14.3	9.3

Figure 7 shows the BGL profile in a day for patient 3 for both clinical and in-silico works similar to the previous two patients. Initially, the BGLs recorded for the clinical and in-silico works were 11.2 mmol/L and 6.9 mmol/L, respectively. Here, one can observe that the postmeal BGLs are similar in both works. Throughout the day, the patient in the clinical work experienced hyperglycemia and was unable to reach the normoglycemic range, with the lowest BGL recorded being only 9.3 mmol/L. Conversely, normoglycemic range for the patient in the in-silico work was achieved 71.43% of the time. The average BGLs for patients in the clinical and in-silico works were 11.00 mmol/L and 6.22 mmol/L, respectively. The highest BGL recorded in the clinical and in-silico works were 14.3 mmol/L and 11.6 mmol/L, respectively.

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Figure 7. Blood glucose profile in a day between clinical and in-silico works for patient 3.



Optimum Bolus Insulin for Blood Glucose Regulations

Bolus insulin is used to control BGL at mealtime. The best time for insulin injection depends on the type of insulin used and the individual's need to achieve optimal BGL targets and reduce diabetes complications. The insulin is typically injected subcutaneously, either with a syringe or an insulin pen, and taken shortly before or after a meal [20]. The amount of bolus insulin needed depends on factors such as age, body weight, the amount of carbohydrates in the meal consumed, insulin sensitivity, and physical activity [21-23]. These factors help patients to determine the appropriate dose of bolus insulin needed.

Patients in the clinical work were given insulin during mealtime as opposed to the in-silico work in which the insulin was injected 30 minutes before a meal. Additionally, it is important to consider the timing of bolus insulin administration. Giving bolus insulin too early before a meal or too late after a meal can result in hypoglycemia and hyperglycemia, respectively. So, the bolus insulin administration was timed appropriately to match the timing of carbohydrate intake.

In this study, all patients used rapid-acting insulin to manage their BGL during mealtime to ensure their BGL would not deviate too far from the normoglycemic range (ie, 4.0-7.0 mmol/L) after each meal. Table 11 summarizes the amount of bolus insulin administered for all patients in the in-silico work.

Table 11. Amount of bolus insulin administered.

Meal	Bolus insulin (mU/min)		
	Patient 1	Patient 2	Patient 3
Breakfast	83.33	66.67	100.02
Lunch	33.33	50.01	83.33
Dinner	16.67	33.33	66.67

Data Analysis for Patients

As for the data analysis of patients between clinical and in-silico works, an MLR was used to model the relationship between meals, insulin, and BGL. The probability value (*P* value) is an important statistical element used to assess the significance of the relationship between these variables as well as to evaluate the accuracy of the simulation results. Table 12 summarizes the data analysis between clinical and in-silico works for all patients.

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Table 12. Data analysis between clinical and in-silico works for all patients.

	P value	
	Clinical work	In-silico work
Patient 1	2.44×10^{-6}	4.17×10^{-7}
Patient 2	3.37×10^{-6}	4.14×10^{-6}
Patient 3	3.72×10^{-7}	9.96×10^{-5}

Discussion

Principal Findings

Observing the BGL trend for all patients in both works, the in-silico work performed better in managing BGLs as compared to the clinical work. Patients in the clinical work rarely achieved the glycemic target, 4.0 to 7.0 mmol/L. Patients 1 and 2 only achieved the target range during the morning and evening, respectively, whereas patient 3 did not achieve the target at all. The patients in the in-silico work were able to achieve the glycemic target more than 70% of the time as compared to the clinical work, which was less than 50% of the time.

The comparison of BGL against time between clinical and in-silico works can be challenging, especially when clinical data is limited, and, in this case, a continuous glucose monitoring (CGM) device is not used. Thus, the BGL profiles are different since patients in the clinical work used conventional methods to monitor their BGL (ie, SMBG and MDI); therefore, only a snapshot of BGLs at a particular time is available for comparison as seen in Figures 5-7. Studies have shown that the use of a CGM device can improve the time in range in clinical settings, thus improving the BGL profiles [24,25].

In this case, the only available data point was the focus since the clinical data was limited and did not cover the entire time span. While BGL simulations can help predict how the BGL of a patient with T1D may change under different conditions, they are not always accurate. This is because the mathematical models used in the simulations are based on assumptions about how the body works, and these assumptions may not always hold for every individual. Additionally, the simulation may not consider all the complex factors that can affect BGLs, such as exercise, stress, or illness. BGL monitoring can also be subjected to errors and variability in clinical settings. Factors such as the accuracy of the glucose meter or sensor, the timing and frequency of measurements, and the variability of patients' responses to interventions (eg, meals, physical activities, and medication) can all affect the reliability and accuracy of clinical BGL monitoring.

Based on Table 11, all patients were injected with more insulin in the morning, and the daily doses continued to decrease. Although the insulin sensitivity varies depending on the time of the day with reduced sensitivity in the evening [26,27], it can be observed that these patients have low insulin sensitivity in the morning; hence, they require more insulin doses to cater to the sudden BGL fluctuation. Patients' insulin sensitivity increases at lunch and dinner, as they require less bolus insulin to regulate the BGL. Despite larger bolus insulin doses given before mealtime, there is still a peak shortly after the meal is consumed, referring to Figures 5-7. Since the time for glucose absorption ($t_{max,G}$=40 minutes) is smaller than the time for insulin absorption to take effect ($t_{max,I}$=55 minutes), the glucose reaches the bloodstream sooner than the insulin, although insulin is infused earlier.

Among all patients, patient 3 injected the most amount of insulin compared to others since patient 3 weighed the heaviest, besides consuming the largest total amount of meals. Since increased body weight decreases insulin sensitivity, the patient's requirement for bolus insulin also increased [28]. In contrast, patients 1 and 2 in the in-silico work required less bolus insulin to control BGLs than patient 3 as they had lighter body weights and consumed meals in smaller portions. Their BGLs in the in-silico work only deviated slightly above the normoglycemic range throughout the day and were relatively more stable.

The probability value or *P* value is a statistical measure that indicates the probability of obtaining the observed results if the null hypothesis is true. The value is between 0 to 1. A *P* value <.05 is often considered statistically significant, meaning there is strong evidence against the null hypothesis, so the hypothesis is rejected. Based on Table 12, all patients in both clinical and in-silico works had a low *P* value (*P*<.001), which indicates that the variables are significant. However, when a comparison was made on the BGL profile, both profiles were not comparable due to different methodologies adopted in the design of the study.

Limitations of the Study

There are two main limitations discovered from the study, which in turn, make it infeasible to address the goal of determining the accuracy and effectiveness of the in-silico model in mimicking real-world BGL dynamics. First, different protocols and conditions were adopted in the methodology for the clinical and simulation works. As stated earlier, the open-loop therapy was used in the clinical work for evaluation purposes, whereas the closed-loop algorithm with eMPC was used in the in-silico test. To address this limitation for future work, it is essential to modify the simulation of the model to make the results more comparable with the clinical data. For instance, it is suggested that in the simulation work, the improved Hovorka equations model could be simulated using the same bolus, basal insulin, and meal carbohydrates used in the clinical trial. By doing so, they could compare the model output with each glucose measurement, preferably when CGM is available at our clinic for future use.

Second, the reported information was insufficient to reproduce the calculation of the optimal bolus in the in-silico simulations. The insulin bolus was computed by trial and error as

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programmed earlier in its closed-loop algorithm. Since one of the main goals of the study is to determine the optimal bolus insulin, it would be advisable to detail the method followed to calculate it in the development of its new control algorithm for future works.

Conclusions

Through in-silico work using the improved Hovorka equations model and eMPC, the optimal amount of bolus insulin required to maintain BGLs within the normoglycemic range for adolescents with T1D has been determined. This approach demonstrates promising potential for precise insulin dosing strategies that aim to achieve stable glycemic control in real-world clinical scenarios. It was observed that patients had less insulin sensitivity in the morning, thus more bolus insulin was administered, and the amount gradually decreased throughout the day. The optimum bolus insulin for patient 1 was 83.33, 33.33, and 16.67 mU/min; patient 2 was 66.67, 50.01, and 33.33 mU/min; and patient 3 was 100.02, 83.33, and 66.67 mU/min for breakfast, lunch, and dinner, respectively.

Based on the comparison of BGL profiles between both clinical and in-silico works, patients in the clinical works experienced hyperglycemia most of the time and achieved the normoglycemic range less than 50% of the time. Conversely, there is a significantly increased time spent in the normoglycemic range for patients in the in-silico works using the improved Hovorka equations model with patients 1, 2, and 3 being in a normoglycemic range 79.59%, 87.76%, and 71.43% of the time, respectively. In conclusion, the in-silico work using the improved Hovorka equations model was not comparable to the clinical works to simulate BGLs with meal disturbances for people with T1D due to different methodologies adopted for both works as well as insufficient information for reproducing the calculation of the optimal bolus in the in-silico simulations. It is therefore recommended to, first, modify the simulation work of the improved model using the same bolus, basal insulin, and meal carbohydrates used in the clinical trial and, second, detail the method followed to calculate it in the development of a new control algorithm for future work.

Acknowledgments

The authors would like to thank the School of Chemical Engineering, College of Engineering, Universiti Teknologi MARA (UiTM) and the Paediatric Department, Faculty of Medicine, UiTM for all the support and assistance rendered. The authors sincerely acknowledge the participation of people with type 1 diabetes in this study.

The authors wish to acknowledge and extend their gratitude to the Ministry of Higher Education, Malaysia, and Research Management Centre, UiTM, for the financial support given under grant 600-RMC/GPK 5/3 (222/2020).

Data Availability

All data sets are presented in the main manuscript.

Authors' Contributions

NAMS conducted the programming work. AMS, NSMN, SAA, and MAA analyzed the data and supervised the overall research. NAMS and AMS wrote the paper.

Conflicts of Interest

None declared.

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Abbreviations

APD: artificial pancreas device
BGL: blood glucose level
CGM: continuous glucose monitoring
EGP: endogenous glucose production

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eMPC: enhanced model-based predicted control
MDI: multiple daily injections
MLR: multiple linear regression
SMBG: self-monitoring of blood glucose
T1D: type 1 diabetes
TDD: total daily dose
UiTM: Universiti Teknologi MARA

Edited by G Eysenbach, T Leung; submitted 19.10.22; peer-reviewed by R Gore, Anonymous; comments to author 17.09.23; revised version received 28.03.24; accepted 01.07.24; published 15.08.24

Please cite as:
Som AM, Sohadi NAM, Nor NSM, Ali SA, Ahmad MA
In-Silico Works Using an Improved Hovorka Equations Model and Clinical Works on the Control of Blood Glucose Levels in People With Type 1 Diabetes: Comparison Study
JMIRx Bio 2024;2:e43662
URL: https://bio.jmirx.org/2024/1/e43662
doi: 10.2196/43662
PMID:

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