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# A Stepwise Approach toward Closed-Loop Blood Glucose Control for Intensive Care Unit Patients: Results from a Feasibility Study in Type 1 Diabetic Subjects Using Vascular Microdialysis with Infrared Spectrometry and a Model Predictive Control Algorithm

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## Abstract

### *Background:*

Glycemic control can reduce the mortality and morbidity of intensive care patients. The CLINICIP (closed-loop insulin infusion for critically ill patients) project aimed to develop a closed-loop control system for this patient group. Following a stepwise approach, we combined three independently tested subparts to form a semiautomatic closed-loop system and evaluated it with respect to safety and performance aspects by testing it in subjects with type 1 diabetes mellitus (T1DM) in a first feasibility trial.

### *Methods:*

Vascular microdialysis, a multianalyte infrared spectroscopic glucose sensor, and a standard insulin infusion pump controlled by an adaptive model predictive control (MPC) algorithm were combined to form a closed-loop device, which was evaluated in four T1DM subjects during 30-hour feasibility studies. The aim was to maintain blood glucose concentration in the target range between 80 and 110 mg/dl.

### *Results:*

Mean plasma glucose concentration was 110.5 ± 29.7 mg/dl. The MPC managed to establish normoglycemia within 105 ± 78 minutes after trial start and managed to maintain glucose concentration within the target range for 47% of the time. The hyperglycemic index averaged to 11.9 ± 5.3 mg/dl.

### *Conclusion:*

Data of the feasibility trial illustrate the device being effective in controlling glycemia in T1DM subjects. However, the monitoring part of the loop must be improved with respect to accuracy and precision before testing the system in the target population.

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**Abbreviations:** (BG) blood glucose, (CHO) carbohydrate, (CLINICIP) closed-loop insulin infusion for critically ill patients, (ICU) intensive care unit, (ITEGA) insulin titration error grid analysis, (IV) intravenous, (MPC) model predictive control, (SC) subcutaneous, (T1DM) type 1 diabetes mellitus

**Keywords:** CLINICIP, MPC algorithm, spectroscopic glucose sensor, tight glycemic control, vascular microdialysis

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## Introduction

Establishing glycemic control can be beneficial for intensive care patients.[1] Glycemic control devices that use the subcutaneous (SC) monitoring route encounter performance difficulties as SC-glucose levels face physiological lag times and low correlation compared to plasma glucose in certain patient groups.[2,3] We therefore developed a vascular-based monitoring and glycemic control device, comprising a body interface for the continuous extraction of blood dialysate,[4] an infrared spectroscopic glucose sensor,[5,6] and a model predictive control (MPC) algorithm[7,8] that generates advice with respect to insulin infusion rates. Following a stepwise approach, these components were performance-tested separately and individually in healthy individuals, patients with type 1 diabetes mellitus (T1DM), and intensive care unit (ICU) patients. In this feasibility trial, we combined these components for the first time to form a closed-loop device. Before approaching the target population, we performed this feasibility trial in T1DM volunteers, evaluating safety and performance issues while trying to establish normoglycemia semiautomatically.

## Research Design and Methods

The 30-hour feasibility studies were performed in four T1DM volunteers (body mass index: 25.8 ± 6.3 kg/m²; age: 31 ± 8 years; three male; diabetes history: 11.4 ± 9.0 years; hemoglobin A1c: 7.2 ± 0.8%) in a supine position. Each subject received four standardized meals (dinner: 6 p.m., snack: 10 p.m., breakfast: 8 a.m., lunch: 12 p.m.) sized 37, 29, 36, and 31 g carbohydrates (CHO), respectively.

Peripheral venous blood was continuously withdrawn from a standard intravenous (IV) line at 2 ml/hour and pumped to an extracorporeal membrane-based microdialyzer by which a protein-free matrix was generated. Dialysate was analyzed further for glucose concentrations using an online infrared spectrometric sensor, with the option to measure further analytes such as lactate, urea, and $pCO_2$ of interest for intensive care medicine. A similar spectrometric system has been successfully demonstrated for plasma glucose monitoring.[9] For our system, average sensor readings were obtained at 5-minute intervals. Every 15 minutes, sensor-derived glucose mean concentration values were entered into a laptop computer running the MPC algorithm.

In the present study, we used a control algorithm based on a MPC paradigm.[10] The algorithm is based on a model of glucose regulation in T1DM described in detail by Hovorka and colleagues.[11] The MPC controller was originally developed and tested in subjects with T1DM[12] and a modified version was used in the critically ill.[8,13] The present study uses the updated controller in a population for which it was originally developed. According to the Leuven insulin titration guideline,[1] the algorithm was initialized to 80 and 110 mg/dl as lower and upper limits of normoglycemia. The suggested insulin dosage was then administered by a standard IV-insulin infusion pump. For safety reasons, only online sensor values within ±20% of reference plasma glucose concentrations were used as input for the algorithm. Otherwise, venous plasma glucose concentrations measured with a Beckman glucose analyzer were used [hypoglycemia: blood glucose (BG) <50 mg/dl].

The study received approval from the Ethics Committee of the Medical University of Graz.

## Results

**Figure 1** shows the subjects' BG concentration profiles and corresponding insulin administration rates. Glycemic control parameters are presented hereafter as mean ± standard deviation. BG could be maintained at a mean BG of 110.5 ± 29.7 mg/dl for all subjects. Day- and nighttime BG averaged 113.4 ± 31.8 and 103.3 ± 22.4 mg/dl, respectively. The peak postprandial glucose concentration was found to be 152.0 ± 33.0 mg/dl (dinner: 135.4 ± 18.4 mg/dl, snack: 141.3 ± 28.7 mg/dl, breakfast: 192.9 ± 17.5 mg/dl, lunch: 138.6 ± 31.5 mg/dl). The hyperglycemic index[14] averaged 11.9 ± 5.3 mg/dl. An analysis according to the grading system presented by Chassin and colleagues[15] revealed that—with respect to the postprandial glucose control (3 h following meal ingestion)—35.2 and 27.1% of the time was spent in grades A and B, respectively (C: 12%, D: 24.4%, E: 0.6%, F: 0.6%). With respect to the outside-meal glucose control, 22.5 and 63.4% of the time was spent in grades A and B, respectively (C: 2.1%, D: 12.1%, E: 0%, F: 0%).

Normoglycemia (80–110 mg/dl) was established 105 ± 78 min after the start of the trial and could be maintained for 47 ± 12% of the trial duration. Two hypoglycemic events were observed (43.4, 49.0 mg/dl), whereof the

former was due to a human error, which resulted from having entered a too high CHO content of the corresponding meal into the algorithm. Both hypoglycemic events were immediately treated with IV glucose bolus administration (10 g each).

Deriving glucose concentrations from the combined body interface online-sensor system failed 24 times (5.4%). The online-sensed glucose concentration values exceeded the critical 20% relative difference to the reference plasma glucose concentration in 8.8% of all cases. Online sensor values differed from the reference plasma glucose concentration by -2.3 ± 14.5 mg/dl on average (relative difference -2.2 ± 13.8%).

A clinical evaluation of the monitoring part (body interface + spectroscopic online sensor) using the insulin titration error grid analysis (ITEGA)[16] revealed that 98.8% of online sensor values led to acceptable treatment, whereas 1.2% caused unacceptable violations.

## Discussion and Conclusions

### *Study Design*

Three subsystems of a closed-loop device for intensive care patients had been developed and performance tested individually in clinical trials involving healthy individuals,[4,5] T1DM patients,[6,7,11,12] and ICU patients[8,13] beforehand. In this feasibility trial, we report on the first combination of these components to form a semiautomatic closed-loop device.

Following a safe and stepwise approach, we performed this first feasibility trial in type 1 diabetic volunteers before leaping toward the target population. From a technical point of view, we neither expected the vascular body interface nor the glucose sensor to perform differently between ICU patients, T1DM patients, or healthy individuals.

The MPC algorithm was originally developed for and tested in subjects with T1DM[12] and was successfully used in the critically ill.[8,13] The present study, therefore, uses the updated controller that has already been proven to work in ICU patients. Given the arguments above and from an ethical point of view, it was thus straightforward to perform this study in T1DM volunteers instead of intensive care patients, allowing us to assess the system's safety and performance characteristics under controlled conditions using evaluation parameters, which apply to intensive care patients.

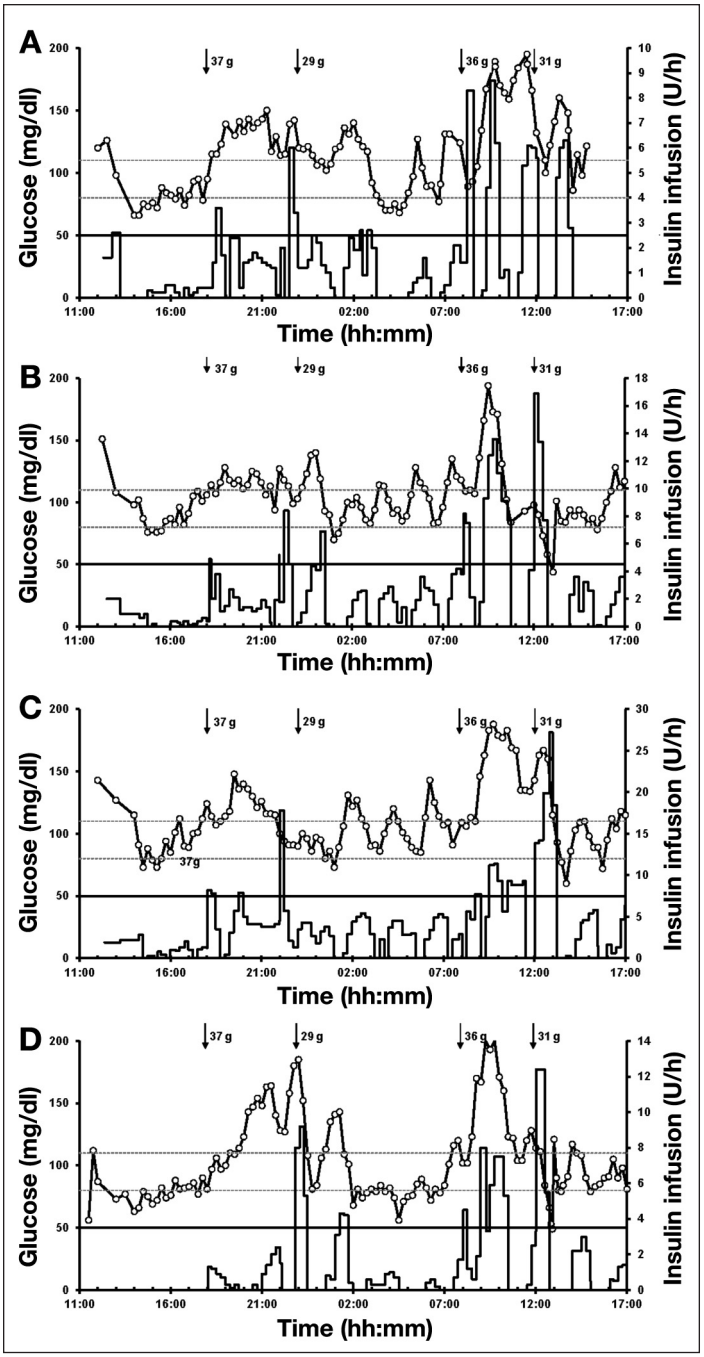


**Figure 1.** Glucose concentration (open circles) and corresponding insulin infusion (black solid lines) time profiles of four T1DM (A–D) in a closed-loop setup using spectroscopic glucose analysis of blood microdialysate and MPC algorithm for insulin titration suggestions. Arrows indicate food intake in gram carbohydrates. Dashed horizontal lines indicate target range for intensive care patients 80–110 mg/dl.[1] The solid horizontal line indicates the hypoglycemic threshold (50 mg/dl).

Due to the pilot character of this study and for safety reasons, we crosschecked online glucose concentration values by comparing them to reference glucose values. It would have been one option then to simply let the MPC work with whatever glucose concentration was

suggested by the online sensor. However, the results of the algorithm's performance evaluation would then have been biased by intermittent erroneous input parameters. Therefore, and again for safety reasons, we implemented a 20% relative-difference threshold for glucose concentration values for steering the algorithm.

### *Technical Performance Evaluation*

The monitoring part of the system (i.e., the combination of vascular microdialysis and online spectroscopic glucose sensor) performed better than previously evaluated technologies[17,18] even though 8.8% of all online glucose concentration levels exceeded critical 20% relative-difference tolerance to the reference plasma glucose concentration. This is a major finding of the study from a technical point of view, which resulted from combining these subcomponents for the first time. The individual errors of the body interface and the spectroscopic online glucose sensor add up to 8.8%, which is satisfactory in our opinion but leaves space for improvement. However, only four subjects were investigated in our trial.

The ITEGA, as well as the hyperglycemic index, as useful measures of glucose control in critically ill patients suggest good glucose control, taking 110 mg/dl as the upper range of normal. Compared to other recently published closed-loop studies in T1DM patients using an SC-glucose monitoring approach,[7,17] our data suggest a better glucose control performance with respect to mean BG, mean daytime, and overnight BG, time in target range (80–110 mg/dl), and percentage of time spent in grade A and B zones of combined postprandial and outside-meal periods. Compared to closed-loop studies using BG measurement and the MPC algorithm in ICU patients,[8,14] our approach performed comparably with respect to time in target and mean BG. With respect to time in target, we report a mean overall time in target of about 47%. Comparing this result to the work of others is quite difficult as to the different natures of study designs, target ranges, etc. A study by Kovatchev and colleagues[19] in T1DM subjects reported that 78% of time spent overnight was within the target range, which was defined as 70–140 mg/dl, whereas in our presented study it is defined as 80–110 mg/dl. If we, however, apply Kovatchev's target range to our data (whole trial period), the total time in target increases to 82.8 ± 5.5%, which is a promising result for this first feasibility trial.

### *Safety Aspects*

Two hypoglycemic events were recorded. The first (BG = 43.4 mg/dl) was caused by a human error, due to an erroneously too high nutrition entry into the MPC algorithm. The second (BG = 49.0 mg/dl) was just below the hypoglycemic threshold and also happened in the postprandial period, allowing us to conclude that the algorithm reacted rather aggressively on enteral nutrition intake. The MPC performance might be improved in that respect if it were provided additional information on the glycemic index of food to take into account the timing, peak, and duration of the glycemic surge.

Nonetheless, the results of this feasibility study are promising and we believe that our approach is worth implementing in an ICU setting, where the MPC algorithm has already proven to work efficiently.[8,13] However, before going into tests within the target population, further technical improvements have to be made and verified with respect to the controller and the monitoring part of the loop. Following our safe and stepwise approach, another series of closed-loop tests must be performed in T1DM subjects, with technical advanced subcomponents before considering first tests in ICU patients.

Another aspect of our measurement setup, which has not been illustrated in this article, is the option for monitoring further intensive care parameters in the critically ill patient, providing new tools for medical treatment.

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