EVALUATION AND IMPROVEMENT OF

AN INSULIN DOSING ALGORITHM

FOR APPLICATION IN A COMPUTERIZED DECISION AND WORKFLOW

SUPPORT SYSTEM

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DOCTORAL THESIS

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GRAZ, MARCH 2016

Statutory declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly indicated all material which has been quoted either literally or by content from the sources used. The text document uploaded to TUGRAZonline is identical to the present doctoral dissertation.

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Preface

This work was carried out at JOANNEUM RESEARCH – HEALTH from October 2012 to March 2016. It summarizes four peer-reviewed journal publications, one book chapter and one patent application which I published as first-author and co-author. In addition, several previously unpublished analyses are presented. For easier readability and to guide the reader through the development process, I decided not to just reprint my already published publications but rather decided to arrange the published and unpublished content in a way to present the "big picture" of my scientific work.

Therefore, some chapters or sub-chapters include reprints of the original manuscripts or parts of the original manuscripts which I clearly state at the beginning of each chapter.

This work is based on the following publications:

JOURNALS

K. Donsa, P. Beck, J. Plank, L. Schaupp, J. K. Mader, T. Truskaller, B. Tschapeller, B. Höll, S. Spat, and T. R. Pieber, "A toolbox to improve algorithms for insulin-dosing decision support.", *Applied Clinical Informatics*, vol. 5, no. 2, pp. 548–56, 2014.

L. Schaupp*, **K. Donsa***, K. M. Neubauer, J. K. Mader, F. Aberer, B. Höll, S. Spat, T. Augustin, P. Beck, T. R. Pieber, and J. Plank, "Taking a Closer Look-Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients with Type 2 Diabetes Mellitus Under Basal-Bolus Insulin Therapy.", *Diabetes Technology and Therapeutics*, vol. 17, no. 9, pp. 611–8, 2015.

*The first two authors contributed equally to this study

K. M. Neubauer, J. K. Mader, B. Höll, F. Aberer, **K. Donsa**, T. Augustin, L. Schaupp, S. Spat, P. Beck, F. M. Fruhwald, C. Schnedl, A. R. Rosenkranz, D. B. Lumenta, L.-P. Kamolz, J. Plank, and T. R. Pieber, "Standardized Glycemic Management with a Computerized Workflow and Decision Support System for Hospitalized Patients with Type 2 Diabetes on Different Wards.", *Diabetes Technology and Therapeutics*, vol. 17, no. 10, pp. 685–92, 2015.

K. Donsa, P. Beck, B. Höll, J. K. Mader, L. Schaupp, J. Plank, K. M. Neubauer, C. Baumgartner and T. Pieber, "Impact of errors in paper-based and computerized diabetes management with decision support for hospitalized patients with type 2 diabetes. A post-hoc analysis of a before and after study.", *International Journal of Medical Informatics*, vol. 90, pp. 58–67, 2016.

BOOK CHAPTERS

K. Donsa, S. Spat, P. Beck, T. Pieber, and A. Holzinger, "Towards Personalization of Diabetes Therapy Using Computerized Decision Support and Machine Learning: Some Open Problems and Challenges.", in Smart Health SE - 10, vol. 8700, A. Holzinger, C. Röcker, and M. Ziefle, Eds. *Springer International Publishing*, pp. 237–260, 2015.

PATENT APPLICATIONS

Insulin dosage proposal system, WO 2015/169814, S. Spat, B. Höll, P. Beck, T. Truskaller, R. Moser, **K. Donsa**, J. Plank, J. K. Mader, K. M. Neubauer, L. Schaupp, T. Pieber, 2015.

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“Reality is frequently inaccurate.”

— Douglas Adams

Evaluation and improvement of an insulin dosing algorithm for application in a computerized decision and workflow support system

DI Klaus Donsa, BSc

Doctoral Thesis

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic disease which highly affects the individual patient and also represents a global health burden with a large financial impact. T2DM patients are common in hospitals and their therapy requires complex and interdisciplinary cooperation of health care professionals (HCPs). Improvement in diabetes management is related to lower rates of hospital complications, but recent evidence suggests that especially therapy regimens involving insulin are prone to error. Driven by the reported medical benefit of improved inpatient glycemic control, the development of GlucoTab® - a computerized workflow and decision support system - was initiated to support HCPs in diabetes management. This thesis is embedded in the development of GlucoTab® and focuses on the evaluation and enhancement of an insulin dosing algorithm for T2DM patients, by using retrospective statistical analysis and simulation.

Important parts of this work address the following topics: 1) development of a framework for data processing, simulation and statistical analysis to evaluate and improve insulin dosing algorithms; 2) evaluation and simulation of modifications/improvements of insulin dosing algorithms; 3) testing the capability of continuous glucose monitoring to assess the clinical impact and safety of basal-bolus insulin therapy; 4) estimating the impact of errors in diabetes management when using either paper-based or computerized decision and workflow support; 5) identification of parameters and methods to select optimal therapy settings and preliminary considerations for the use of machine learning and decision support in the personalization of diabetes therapy.

Computerized algorithm-based decision support systems directly influence clinical practice and have the potential to achieve significant and clinically relevant improvements. The data analyses in this PhD thesis show that such systems reduce errors and therefore decrease the probability of patients experiencing hypo- and hyperglycemia, but a potential for errors still remains. Ways to further reduce error potential and to further improve insulin dosing algorithms in computerized diabetes management systems are discussed.

KEYWORDS

Computerized decision support systems, workflow support, medication management systems, diabetes management, medication errors, type 2 diabetes mellitus, simulation, evaluation, clinical impact, basal-bolus insulin therapy, dosing algorithms, continuous glucose monitoring

ABBREVIATIONS

ADA	American Diabetes Association
BG	Blood glucose
CDSS	Computerized decision support system
CE	Conformité Européenne
CGM	Continuous glucose monitoring
CV	Coefficient of variation
DM	Diabetes mellitus
ETL	Extract transform and load
ETR	Extended target range
FDA	Food and Drug Administration
GDD	Good diabetes days
GV	Glycemic variability
HbA1c	Glycated hemoglobin
HCPs	Health care professionals
ICU	Intensive care unit
IEC	International Electrotechnical Commission
IU	Insulin unit
ML	Machine learning
NN	Neural networks
POCT	Point of care testing
RCT	Randomized controlled trial
RMSE	Root mean square error
SD	Standard deviation
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TDD	Total daily dose

CONTENTS

CHAPTER I

Introduction – Setting the scene

This chapter provides an introduction and is setting the scene for my scientific endeavors to evaluate and improve inpatient treatment of type 2 diabetes mellitus patients using a computerized workflow and decision support system. It also describes the objectives of this PhD thesis and how this work contributed to the development of GlucoTab®

1. Inpatient diabetes management is in the need of improvement

Diabetes mellitus (DM) is a chronic illness of the metabolic system leading to high blood glucose (BG) levels. DM can be classified into two main clinical categories. Type 1 diabetes mellitus (T1DM) is caused by the loss of β-cells which are responsible for the storage and release of insulin and it mainly occurs in children, adolescents and young adults. In contrast, type 2 diabetes mellitus (T2DM) is determined by insulin resistance and develops due to a progressive insulin secretory defect, mostly in elderly people with overweight or obesity [1]. In both conditions continuous medical care is required to minimize the risk of acute (e.g. ketoacidosis) and long-term complications (e.g. diabetic foot syndrome, nephropathy, retinopathy, cardiovascular diseases or stroke) [2]. T1DM can only be treated with insulin, whereas a wide range of therapeutic options are available for patients with T2DM [1]. Adhering to therapy in chronic diseases like DM requires active participation and is often very burdensome for patients. Long-term complications take years to develop and the effects of a poor controlled disease are not immediately evident in T2DM. Unfortunately, this does not promote the adherence to therapy. [3]

DM is a growing global disease which highly affects the individual patient and also represents a global health burden with financial impact on national health care systems. In 2013 approximately 382 million people were suffering from diabetes. It is estimated that in 2035 this number will reach 592 million. In the United States of America, the total estimated costs for diabetes were $174 billion for the year 2007. The largest component of medical expenditures attributed to diabetes is hospital inpatient care ($58 billion). [4], [5]

Around 20% of hospital inpatient days occur in patients having DM [5]. Over 90% of DM patients admitted to hospitals have T2DM [6]. According to estimates from the United Kingdom, inpatients with recorded DM stay up to 100% longer on average, are 50% less likely to be treated as day cases and are almost 100% more likely to be readmitted as an emergency [4]. These patients require a higher intensity of care which causes considerable additional costs [7]. The higher intensity of care is partly attributable to higher severity of illness, as patients with diabetes often have several comorbidities which leads to an increased risk to experience adverse events during hospital stay [8]–[10].

Observational and randomized controlled studies indicate that improvement in diabetes management results in lower rates of hospital complications in general medicine and surgery wards [11], [12]. However, in-hospital diabetes management is often flawed. In a recent diabetes inpatient audit, 37% of

diabetes patients experienced at least one diabetes medication error during hospitalization and were more than twice as likely to have one or more severe hypoglycemic episodes [6].

Diabetes management requires complex and interdisciplinary cooperation of health care professionals (HCPs) involving ordering doses and correction schemes, BG measurement and timely administration of resulting insulin doses. To support this complex process recently published guidelines and studies recommend the use of computerized decision support systems (CDSS) [8] and medication order entry systems for diabetes therapy in hospitalized patients [13]–[15]. The combination of medication order entry systems and CDSS has proven to reduce medication errors but clear evidence that this combination reduces clinical adverse drug events is still missing [16].

Current evidence supports proactive, scheduled insulin regimens for any patient with consistent hyperglycemia, not only patients with known diabetes and/or who were taking insulin before hospitalization [17]. Therefore, international diabetes experts recommend a structured approach and an algorithm-driven basal-bolus insulin regimen in hospitalized T2DM patients [1]. This regimen involves long-acting insulin to supplement basal insulin requirements during periods of fasting and separate injections of rapid-acting insulin to prevent rises in BG levels resulting from meals. Insulin dosing algorithms aim to achieve BG levels in a desired range by accounting for meals and unphysiological BG levels.

At present, personalization of T2DM therapy in hospitals plays a secondary role due to three factors: 1) A short length of stay does not allow the empiric development of patient-specific factors which are crucial for the personalization of diabetes therapy. 2) Rigid hospital workflows and excessive workload of HCPs often prohibit the implementation of individualized diabetes therapies. 3) Diabetes therapy regimens allowing personalization are complex and very often hospital wards are lacking the know-how to implement them safely and effectively. Therefore, a sliding-scale insulin therapy regimen is still often used in hospitals, because it is easy and convenient for the medical staff to administer, even though it is known that it does not control BG very well [18]. Management of T2DM is therefore very generic and is designed to operate safely for the majority of patients. Nonetheless, aside from these restrictions personalization is possible to some extent and is recommended by current guidelines [1].

2. Start of the GlucoTab® development process

Although considerable efforts have been made to improve glycemic management, an adequate insulin therapy in clinical practice is still lacking in many hospitals despite its recommendation by diabetes experts and guidelines [19]. Contradictory to these recommendations, the management of T2DM in hospitals with insulin compares poorly to non-insulin therapy options by using different outcome measures. Comparing these diabetes management options is problematic because they target different patient populations, but recent evidence demonstrated that by using insulin in T2DM therapy, patients had significantly more medication errors, more hypoglycemic episodes and poorer glycemic control [6].

As part of the 7th European Commission framework-program project REACTION (Remote Accessibility to Diabetes Management and Therapy in Operational healthcare Networks) inpatient diabetes management was identified as important field for improvement. Therefore ways for improvement were sought and as consequence the development process of a mobile computerized workflow and decision support system was initiated. In an initial clinical data review an insulin dosing regimen for basal-bolus insulin therapy in hospitalized T2DM patients was identified which demonstrated good glycemic control in non-critical care [20], [21]. This regimen involved subcutaneous insulin injection of long- and rapid-acting insulin. Insulin dose calculations were based on four BG measurements (three pre-meal and one bedtime) and consisted of insulin for meals and supplemental insulin for high BG levels. It furthermore included a structured rule-based therapy initialization and a daily rule-based therapy adjustment. The therapy protocol used in the original study is provided in Appendix III – Supplemental Material (Initial insulin treatment protocol).

This basal-bolus insulin regimen was customized to account for complex processes during inpatient care and was then integrated into the workflow of a general internal medicine ward [22]. In a proof-of-concept study the efficacy, workflow integration and usability of a paper-based protocol for basal-bolus insulin therapy in T2DM patients was assessed, and it served as data basis for improvements of the insulin dosing algorithm. The workflow-integrated algorithm for basal-bolus therapy was effective in establishing glycemic control compared to standard care and was well accepted by medical staff, but room for improvement was discovered.

In an interdisciplinary development process the paper-based protocol was translated into a computerized system for workflow and decision support. This system aims to overcome shortcomings

of manual procedures. Specifically in preventing input-, calculation- and double data-entry- errors, and providing automated therapy visualizations and traceable real-time documentation for time-critical tasks.

The result of this development process is GlucoTab® - a mobile computerized client-server system, supporting HCPs in diabetes management of hospitalized T2DM patients directly at the point of care. The main function of the system is the provision of insulin dose recommendations for basal-bolus insulin treatment of T2DM patients. GlucoTab® is a CE marked medical device software (Class I, risk class C according to IEC 62304). It comprises the following functionalities which aid physicians and nurses: 1) medication order entry with insulin dosing decision support for physicians, 2) workflow management for physicians and nurses, 3) data entry at the bedside and 4) drug administration support including insulin dose calculation for nurses. The GlucoTab® process is displayed in **Figure 1**. The mobile system assists in organizing the treatment workflow, including display for open tasks, facilitating documentation and providing visualization of BG values, nutrition and insulin doses.

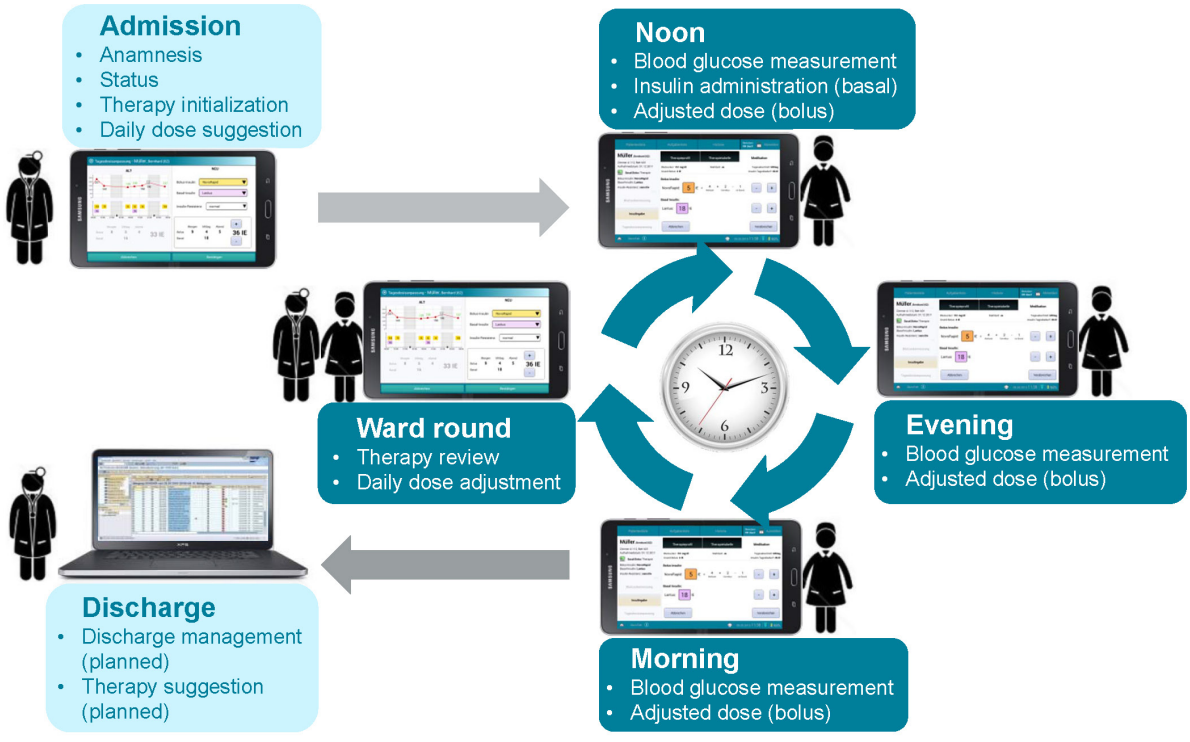

Figure 1: The GlucoTab® process - therapy workflow for basal-bolus therapy in hospitalized T2DM patients. The BG measurement and the potential supplemental bolus insulin injection at night are not displayed

In the GlucoTab® process dosing decisions are based on four daily capillary BG finger-stick measurements (three pre-meal and one bedtime measurement). Additional BG measurements are performed if deemed necessary by HCPs. The system is used to calculate the initial total daily dose

(TDD) of insulin based on the patient's weight, age and renal function (serum creatinine level) as well as to calculate a new TDD for the next 24 hours based on the previous TDD and BG values of the preceding 24 hours. The calculated TDD is either accepted or modified by the physicians and is then divided into a 50% daily basal and a 50% daily bolus insulin dose. The bolus dose is distributed among the three meals (breakfast, lunch, dinner). In case pre-meal BG values are below the target range the insulin bolus is reduced, whereas BG values above the target range induce an increased bolus dose. In most patients the basal-bolus insulin algorithm aims for fasting and pre-meal BG levels of 100 – 140 mg/dL. In case of supplemental insulin suggested due to high BG, the algorithm further adjusts the dose using an insulin sensitivity parameter. Insulin sensitivity (sensitive, normal and resistant) is assessed by the attending physician during each morning round. Additional bolus injections are performed if deemed necessary by the HCPs. This diurnal interdisciplinary workflow, the standard measurement times and time of interventions are displayed in **Figure 2**. In the GlucoTab® process continuous glucose monitoring (CGM) is not used routinely but was used in a subgroup of patients to investigate the patients' glycaemia in more detail.

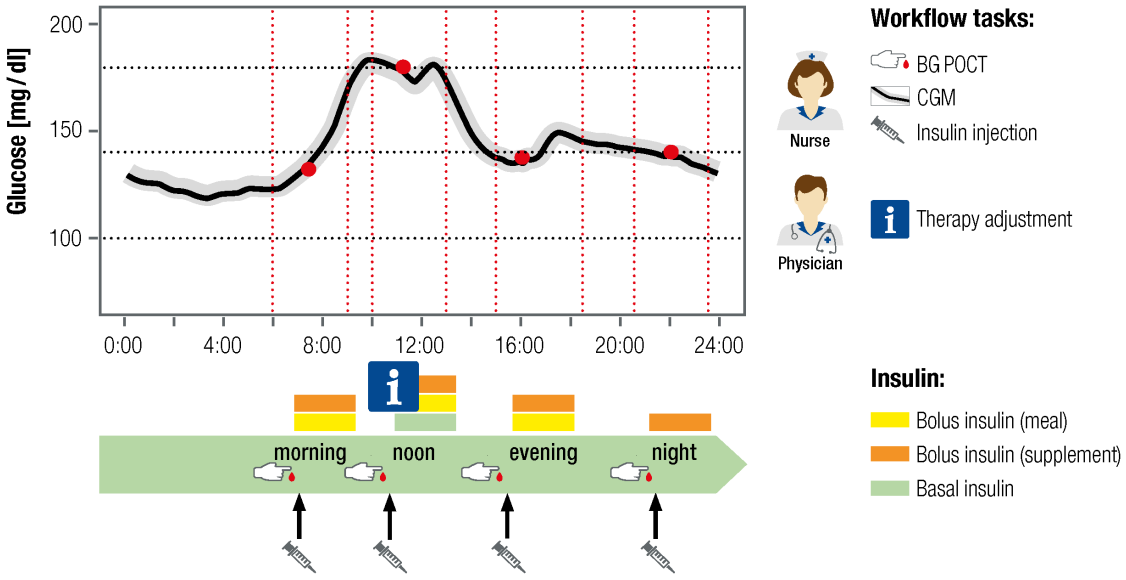

Figure 2: Diurnal interdisciplinary treatment workflow of GlucoTab®. BG POCT…Blood Glucose Point of Care Testing, CGM … Continuous Glucose Monitoring

In the course of the development of GlucoTab® several areas of improvement were identified. These areas ranged from - improvement of technical components of the system, like user management integration from the hospital active directory etc. - to the support of new therapy regimens using different insulin analogues. A central area for improvement was the decision support component of

GlucoTab® and its' underlying rule-based insulin dosing algorithm. In combination with the workflow management component there were many already known and unknown factors influencing the performance of the system regarding safety and effectiveness. The analyses in this PhD thesis target the evaluation and improvement of the insulin dosing algorithm used in GlucoTab®, by using simulation and retrospective statistical analysis of data from clinical studies.

3. Objectives and research questions

The analyses in this PhD thesis were targeting in a holistic way the evaluation and improvement of the insulin dosing algorithm used in GlucoTab®. Therefore the objectives of this thesis were structured as follows:

Development of a framework for data processing, simulation and statistical analysis: Reusable tools and methods had to be developed to import and pool data from different studies for evaluation of safety and effectiveness of the GlucoTab® system and to allow a standardized integration of data from future clinical studies. This framework had to be able to test and evaluate modifications/improvements of the insulin dosing algorithm prior to implementation into GlucoTab® using a workflow simulator. The impact of the modification on the patients' BG levels had to be estimated and displayed. As part of this PhD thesis following research questions were addressed: How to measure glycemic control? How to measure the performance of an insulin dosing algorithm?

Evaluating modifications of the insulin dosing algorithm: The impact of modifications of the insulin dosing algorithm had to be evaluated using simulation and retrospective statistical analysis. As part of this PhD thesis following research question was addressed: Did the implemented modifications of the insulin dosing algorithm have the intended beneficial effect on the patients' diabetes therapy regarding safety and effectiveness?

Testing the capability of continuous glucose monitoring (CGM) to assess the clinical impact and safety of basal-bolus insulin therapy: A four point daily glucose profile is capable of safely running a basal-bolus insulin algorithm. However, it does not picture the diverse glucodynamics of patients with diabetes, in particular during the patient's reconvalescence with various factors influencing the carbohydrate metabolism. CGM could be useful to display the complete diurnal glycemic profile and detect patterns of responsiveness to therapeutic efforts using GlucoTab®. As part of the dissertation following research questions were addressed: Are we missing something by solely using BG spot

measurements for therapy decisions? Is a four point measurement scheme and the standard measurement times (pre-meal and bedtime) adequate for decision making? Could the use of CGM be justified for running a basal-bolus insulin algorithm for T2DM patients on a clinical ward?

Evaluation of the workflow and decision support system regarding safety, efficacy and usability: The final version of GlucoTab® was evaluated in a clinical study on different wards. Additionally, the diabetes management was investigated on a patient subgroup level. As part of this PhD thesis following research question was addressed: Are there subgroups of patients where the diabetes management is not working well using GlucoTab®?

Clinical benefits of computerized workflow and decision support: In the course of the GlucoTab® development, a basal-bolus insulin regimen was first tested in a paper-based way and was then implemented into GlucoTab®. The research questions addressed by this PhD thesis targeted the investigation of medication errors in paper-based and computerized clinical decision and workflow support. The analysis of medication errors related to inpatient diabetes management should lead to the detection of possible improvements and should justify the use of computerized systems for insulin dosing.

Personalization of the GlucoTab® algorithm - Preliminary considerations: Patient-centered care and standardized algorithmic management are conflicting approaches. Individualization of the patient's diabetes therapy is often in conflict with the rigid workflows on clinical wards. The investigations in this PhD thesis targeted the identification of parameters and methods to select optimal therapy settings in diabetes therapy. Preliminary considerations for the use of machine learning and decision support for personalization of diabetes therapy were performed.

4. Structure of the thesis

This thesis is organized in the following structure, addressing the objectives of this scientific work in distinct chapters. Each chapter is based on peer-reviewed articles published as first-author or as co-author and is discussed in a summary section at the end of each chapter. My work started with data processing and initial statistical analyses of data from clinical studies related to the development of GlucoTab®. Already in an early phase of my work the necessity to develop a framework for data processing, simulation and statistical analysis was evident. Chapter II explains the purpose and benefits of this framework. Chapters III to V summarize evaluations of the insulin dosing algorithm

improvements in different stages of the development. Chapter III deals with evaluations of algorithm modifications and Chapter IV summarizes evaluations testing additional CGM for assessing the clinical impact of a basal-bolus insulin regimen. Chapter V demonstrates the results of a study investigating safety, efficacy and usability of using the current version of GlucoTab® on different clinical wards. The clinical benefit of computerized workflow and decision support is investigated by a post-hoc analysis of a before and after study comparing medication errors in paper-based and computerized workflow and decision support in Chapter VI. Chapter VII addresses preliminary considerations for the use of machine learning and decision support for personalization of diabetes therapy. In the end the results of the previous chapters are discussed and directions of future research are outlined (Chapter VIII).

CHAPTER II

Development of a framework for data processing, simulation and statistical analysis

This chapter is partly taken from a previously published article (**Donsa** et al. 2014, [23]) and is complemented by so far unpublished data. Here, the developed framework which is basis for further analyses presented in this PhD thesis is described.

1. How to measure the level of glycemic control?

The purpose of diabetes therapy is to mimic physiological BG profiles as close as possible which means to avoid unphysiologically high and low BG levels. There are several ways to measure the success of diabetes therapy (the level of glycemic control) using short- and long-term parameters or metrics. All short-term parameters and metrics are also usable as long-term measures if averaged over a certain period of time. This section provides the most common parameters and metrics and describes why the development of new ways for measuring the level of glycemic control was necessary in improving the insulin dosing algorithm used in GlucoTab®.

Long-term parameters: A measure of compliance with diabetes therapy is provided by the level of the patients' *glycated hemoglobin (HbA1c)*. It is a laboratory parameter which serves in specific situations as a biomarker for the *average BG levels* in patients over the previous 2 to 3 months prior to the measurement. Several analyses have shown a strong correlation between HbA1c and the patients' average BG levels, with each 1% (10.9 mmol/mol) change in HbA1c corresponding to a change of ~35 mg/dL (1.9 mmol/L) [24]. In DM, higher average BG levels have been associated with increased risk for microvascular complications (nephropathy, retinopathy) and to a lesser extent with macrovascular complications [3]. Even though HbA1c serves as a good indicator for average BG levels based on pre-meal BG levels it does not provide any information on short-term hypo- and hyperglycemia [24].

Short-term parameters and metrics: The level of appropriate glycemic control and therefore the BG targets of diabetes therapy are strongly influenced by the setting in which the therapy occurs. For non-critically ill hospitalized DM patients a *target BG* of less than 140 mg/dL (7.8 mmol/L) for pre-meal BG levels and less than 180 mg/dL (10.0 mmol/L) for a random BG measurement is recommended by the American Diabetes Association (ADA) if patients are treated with insulin. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe co-morbidities. Therapy targets should only be realized if these targets can be safely achieved [1]. The ratio of BG measurements in a well-defined *target range* (e.g. 100 – 140 mg/dL) serves as measure for glycemic control.

Hypoglycemia is feared by patients as well as HCPs and must be avoided in safe and effective diabetes therapy. A plan for preventing and treating hypoglycemia should be established for each patient and episodes in the hospital should be documented and tracked [1]. Documented symptomatic- and asymptomatic hypoglycemia are defined as occurring at a plasma glucose concentration of <70 mg/dL

(3.9 mmol/L) [25]. This BG level remains a common threshold for defining hypoglycemia, but there are also other thresholds defined. Frequent hypoglycemia serves as an indicator for the necessity to adjust the therapy.

Glycemic Variability (GV) is the fluctuation of the patients' BG values and it is used as an indicator for the quality of diabetes management, as a high GV leads to increased risk of hypo- and hyperglycemic episodes [26]. Numerous metrics have been defined in the last decades, especially for CGM. Most notably are: (1) SD_T (total variability in a data set), (2) SD_w (the average of the SDs within each day), or (3) MAGE (average amplitude of up-strokes or down-strokes with magnitude greater than 1 SD), as a measure of within-day variability, and (4) $SD_{b\ hh:mm}$ (average of all SDs for all times of day), or (5) MODD (mean difference between glucose values obtained at the same time of day on two consecutive days under standardized conditions) as a measure of between-day variability. [27]

Good diabetes days (GDD) are a relatively new concept for measuring the level of glycemic control and the "quality" of the BG measurement process. In the national diabetes inpatient audit in Great Britain a good diabetes day is defined as when the frequency of BG monitoring was appropriate, there was no more than one BG measurement of 11 mmol/L (198 mg/dL) or greater and no BG measurements of less than 4 mmol/L (72 mg/dL). Appropriate BG testing was defined as four or more times a day for patients who are unwell or have unstable diabetes or who are on a basal-bolus insulin regimen; twice a day or more for patients on insulin, Exenatide, Sulphoyurea or more than one oral hypoglycemic agent including DPP4-inhibitors and Glitazones; once a day or more for patients on Metformin or diet management alone; or once a week or more for long stay patients with stable control [28].

A comprehensive assessment of the level of glycemic control was a prerequisite for seeking improvements of the insulin dosing algorithm used in GlucoTab®. While these already established long- and short-term parameters or metrics serve as a good basis for investigating the overall level of glycemic control they were not designed to measure the performance of an insulin dosing algorithm. The link between cause (algorithm component: e.g. bolus insulin dose calculation) and effect (e.g. hypo- and hyperglycemia or GV) is often difficult to establish. Therefore new metrics for evaluating safety and effectiveness of the insulin dosing algorithm had to be developed.

1.1 From individual to pooled evaluation of safety and effectiveness of diabetes therapy

Graphical interpretation of glucose and insulin therapy proofed to be very helpful for individual assessment of the patients' diabetes therapy. Especially at the beginning of the GlucoTab® development, safety and effectiveness of diabetes therapy were discussed with diabetes experts on a patient individual basis. **Figure 3** displays glycemic and therapy information of one patient day of a patient treated with the initial version of the GlucoTab® algorithm. A graphical demonstration of the patients' diabetes therapy systematically displays the level of glycemic control and the impact of the therapy is immediately observable. Unfortunately, graphical demonstration lacks the objective interpretation using single metrics or parameters for measuring the level of glycemic control. Therefore, a penalty scoring system proofed to be a valuable tool for investigating the level of individual glycemic control. The penalty scoring system evaluates the therapy of each patient considering the average BG levels, hypo- and hyperglycemic events and GV. If the patient's glycaemia was within the target range the scoring system rewards credit points whereas BG values outside the target range are given penalty points. Penalty points are weighted according to the severity of hypo- or hyperglycemia. Hypoglycemia has a higher impact on the score. For comparisons of safety and effectiveness of different versions of insulin dosing algorithms using retrospective workflow simulations and BG estimations (see chapter 2.3 – Simulation), the impact of algorithm modifications is measurable with a single score for each patient. The score is very sensitive to hypoglycemic events which reduces this blind spot which is present for example by evaluating glycemic control using only the patients' average BG.

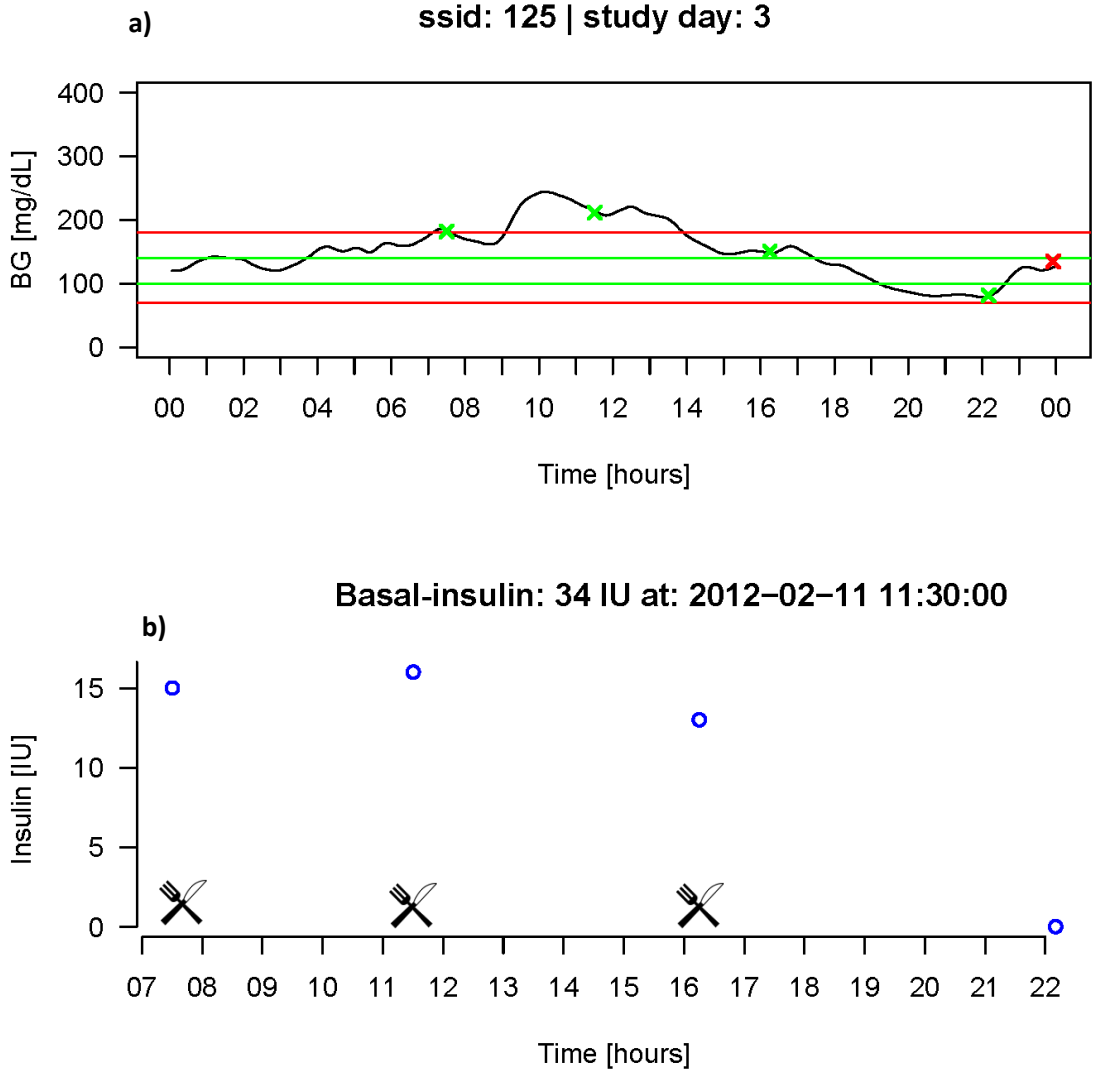

Figure 3: Diurnal glycemic profile and course of diabetes therapy. **(a)** Green crosses indicate scheduled BG measurements; red crosses indicate additional control measurements. The continuous course of BG is displayed with continuous glucose monitoring. **(b)** Basal insulin administration is shown as text and blue circles indicate scheduled bolus injections. The knife and fork symbol indicates if a meal was planned

This penalty scoring system worked very well to detect potential safety issues by "in-silico"-testing new versions of the insulin dosing algorithm, but it lacks the level of detail for providing overall information of the level of glycemic control. For this purpose the already established parameters and metrics were very helpful. **Figure 4** shows the diurnal glycemic profile of a patient cohort treated with GlucoTab® and monitored with additional CGM. This graphical presentation of glycemic control was inspired by the recommendations of Bergenstal et al. for standardizing the analysis and presentation of glucose monitoring data [29].

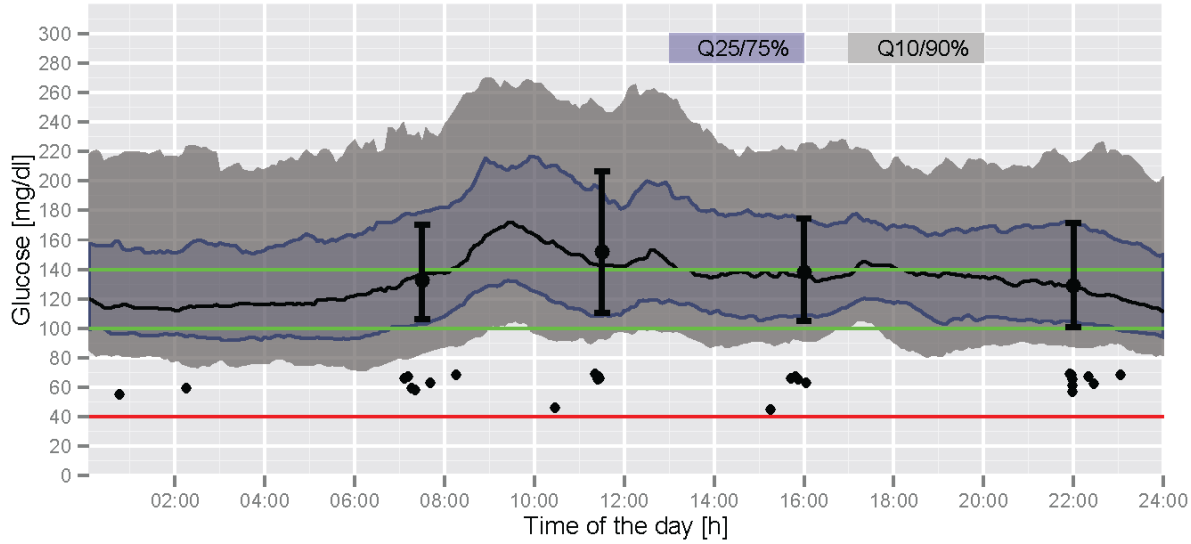

Figure 4: Diurnal continuous glucose monitoring (CGM) profiles and reference blood glucose (BG) measurements (35 T2DM patients). CGM values are median – interquartile range (25–75% [Q25/75%] and 10–90% [Q10/90%]). BG values are median – interquartile range (25–75%), displayed as bars. Black dots indicate hypoglycemic events (<70 mg/dL). Data from Neubauer et al. 2015 [30]. Q … quantile; h … hour

Figure 5 demonstrates BG levels in predefined ranges as a function of treatment days. This method allows a very comprehensive evaluation of the progress of diabetes management and therefore to measure the level of glycemic control. In the course of this PhD work a multitude of customized graphic output functions has been developed or adapted to evaluate the safety and effectiveness of diabetes therapy using GlucoTab®.

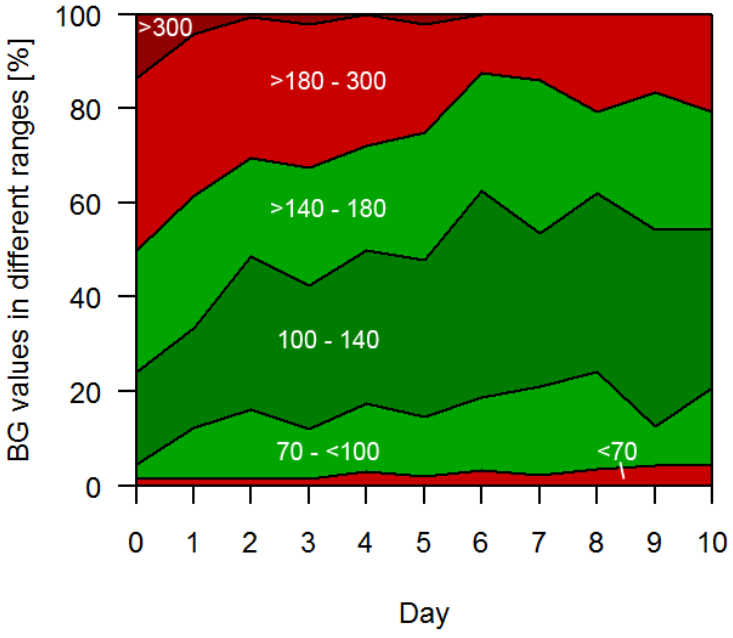

Figure 5: Distribution of BG values in predefined ranges of 37 T2DM patients treated with the initial version of the insulin dosing algorithm (<70, 70-100, 100-140, 140-180, 180-300, >300 mg/dL) as a function of the treatment days. Data from Mader et al. 2013 [22]

1.2 Evaluation of safety and effectiveness of the insulin dosing algorithm

A method was developed to evaluate the "success" of individual decision support steps and to interpret them in an aggregated form, **Figure 6**. The focus of this development was to investigate safety and effectiveness of GlucoTab® in general, and specifically to investigate the algorithm component calculating supplemental insulin (correction insulin) for too high BG levels. The intervention borders of the supplemental insulin scheme are displayed on the x-axis. Higher BG levels are associated with an increase of the supplemental insulin dose. For each intervention border the patients' BG levels at the start and at the end of the observation period are demonstrated on the y-axis. Each line demonstrates two BG measurements and one decision support suggestion. By including additional information such as the BG measurement interval (e.g. morning-noon etc.) the data is accessible in an aggregated form for the interpretation of trends. The proportion of "successful" titrations into the extended target range (ETR) ranging from 70 to 180 mg/dL is additionally demonstrated. Especially for subgroup analyses this method provides very detailed information on the level of glycemic control.

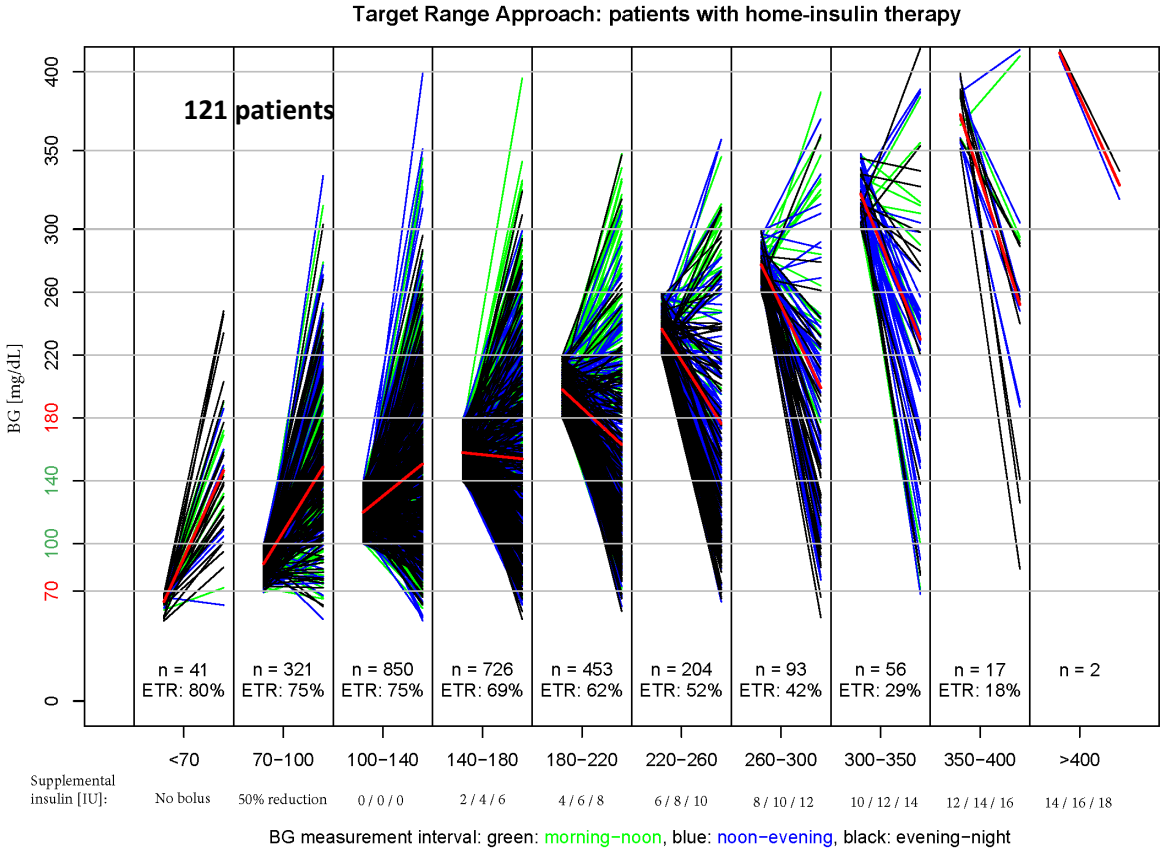

Figure 6: Target range approach: Evaluation of safety and effectiveness of the insulin dosing algorithm: The red line is the mean of all lines within an intervention border. Supplemental insulin dose according to blood glucose intervention border (mg/dL) and insulin sensitivity [sensitive / normal / resistant]; IU … Insulin Unit, ETR … Extended Target Range (70-180 mg/dL)

2. A toolbox to improve algorithms for insulin-dosing decision support [Donsa et al. 2014]

The aims of this framework/toolbox development were: to improve the GlucoTab® algorithm which in its initial form lacked flexibility, to test and optimize new ideas and hypotheses for algorithm modifications to draw maximum benefit from future clinical studies, and to identify individualized algorithm and workflow improvements for specific patient subgroups. We have now incorporated several heterogeneous clinical data sources and implemented a standard procedure for statistical analysis. This section summarizes the methods and technologies and the iterative process used to develop the toolbox for improving algorithms for insulin-dosing decision support.

The toolbox consists of three main components (**Figure 7**):

1. **Data preparation**: Data from several heterogeneous sources is extracted, cleaned and stored in a uniform data format.
2. **Analysis:** The algorithm performance is measured and visualized for all patients or patient subgroups.
3. **Simulation:** Modified versions of the algorithm are applied in simulations of the treatment workflow, based on real data from clinical studies.

2.1 Data preparation

The purpose of this component is to extract, transform and load (ETL) data from clinical studies and other sources into a uniform data structure in a standardized process. One major challenge in the performance of pooled data analyses is the varying structure of data from different clinical studies. We designed a multi-step process to monitor and clean the data: the first steps are performed routinely as part of clinical study data management according to Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) [31]. In each clinical study data is extracted from the sources and transformed into a standardized format according to standard data management: data is first checked for consistency and quality; applying for example summary statistics and row checks in the form of if-clauses. Inconsistent, implausible or missing values are discussed with the clinical study team in the database release meeting to achieve a clean dataset for statistical analysis. As part of the toolbox, during the data preparation step, the data is extracted, cleaned and stored in a uniform data format for pooled statistical analyses. Type and unit conversions as well as preparations for the simulations and analyses

are performed in this step. Patient-specific profiles with baseline characteristics, concomitant diagnoses and medications, overall glycemic information (mean BG levels, glucose variability, hypo- and hyperglycemic events) and information on the algorithm version used are generated. "Virtual insulin sensitivity" profiles are also generated which are required for BG estimations, performed in the simulation component (see section 2.3 Simulation).

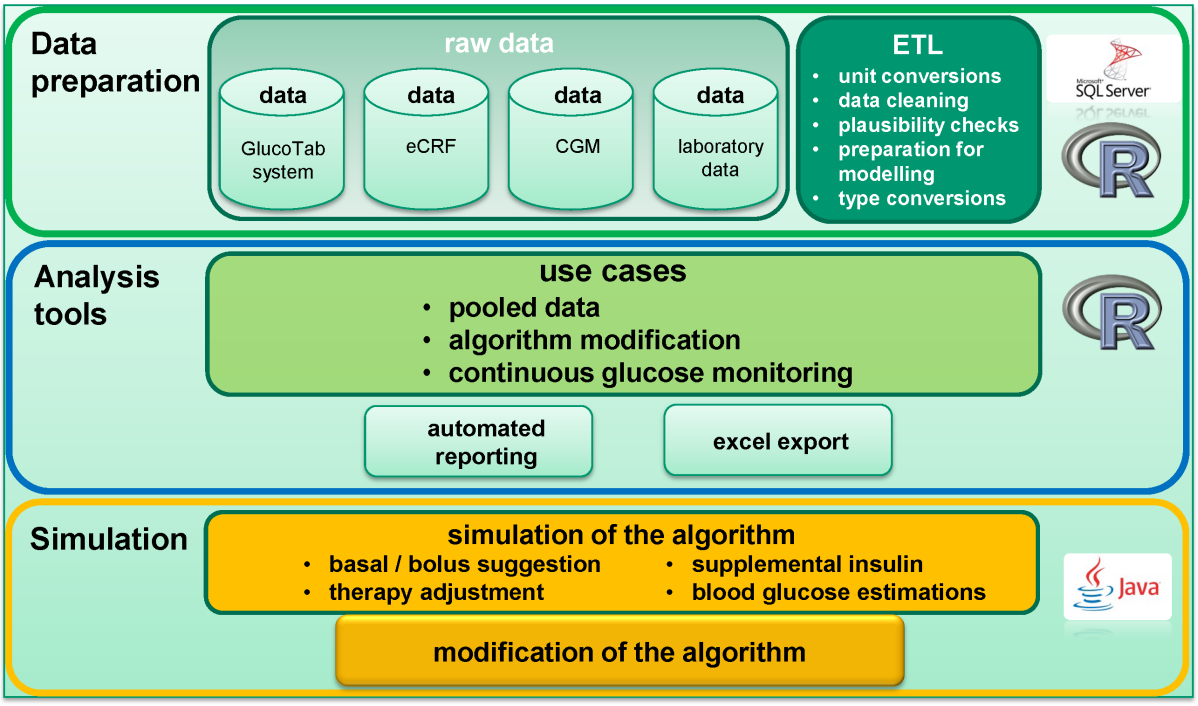

Figure 7: Structure of the toolbox for improving algorithms for insulin-dosing decision support. ETL … Extract, Transform and Load

2.2 Analysis

In the analysis component, different methods of the toolbox (e.g. patient hazard analysis, what-if analysis) are combined depending on the specific research question. Results from the analysis component are summarized in a reporting tool. The following use cases demonstrate the possibilities of the toolbox by using data from three clinical studies and comprise datasets from the following data sources:

- **GlucoTab® server:** 5,218 BG measurements (Roche Accu-Chek) from 166 patients on 1,124 patient days, suggested and confirmed bolus and basal insulin doses and information on consumption of meals and insulin sensitivity

- **Clinical study data management system (OpenClinica):** Diagnoses, medications and baseline characteristics of 166 patients
- **Laboratory information system:** Hospital laboratory data of 99 patients
- **Continuous Glucose Monitoring (CGM):** 14,140 hours recorded with CGM (Medtronics iPro®2) of 97 patients

Pooled data: The first use case demonstrates methods for the retrospective analysis of pooled patient data. It aims to detect the quality of glycemic control when using the GlucoTab® system by identifying individualized versions of insulin-dosing algorithms for specific patient subgroups. A penalty scoring system evaluates the therapy of each patient considering the average BG levels, hypo- and hyperglycemic events and glucose variability. If the patient's glycaemia is within the target range the scoring system rewards credit points whereas BG values outside the target range are given penalty points. Penalty points are weighted according to the severity of hypo- or hyperglycemia. Hypoglycemia has a higher impact on the score. Subgroup analyses using hierarchical clustering allow the detection of "responder" or "non-responder" patient subgroups and their distinctive properties.

Algorithm modification: The second use case aims to evaluate algorithm modifications. In what-if analyses, outcomes regarding BG levels and suggested insulin doses are investigated and visualized for interpretation by clinical specialists. Patient hazard analyses for patients with low glycemic events are performed to identify the safest version of the modified algorithm: insulin dose calculations are simulated by using new variants of the algorithm. To detect potentially dangerous changes in the algorithm, a potential increase of insulin doses prior to a low-glycemic event is investigated. Patient hazard analyses are discussed with diabetes specialists to ensure that only safe variants of a new algorithm are finally implemented.

Continuous glucose-monitoring data: The third use case considers additional input from continuous glucose monitoring (CGM) data for algorithm evaluation. The clinical standard for monitoring the patient's BG levels is point of care testing (POCT) [32]. However, POCT provides only a snapshot of the patient's glycemic profile. With the use of CGM we investigated if these snapshots are sufficient for the patient's therapy. We identified low- and high glycemic episodes using CGM data. Another aim is to relate CGM to the algorithm: in a subsequent what-if analysis the patient's outcome is investigated regarding suggested insulin doses and patient hazard.

The **reporting tool** generates automated PDF reports using the R-project for Statistical Computing [33] with Sweave and LaTeX. A multitude of customized graphic output functions has been developed using ggplot and ggplot2 packages. Results can be reported as text, tables or figures by using the customizable PDF reports.

2.3 Simulation

Simulation aims to estimate the effect of insulin dose changes on BG values due to algorithm modifications. Simulations are performed with a simulator application implemented in Java which integrates and uses original components from the GlucoTab® server implementation. This approach was chosen because building on the original and well tested medical device software components is much more reliable and resource-effective compared to completely rebuilding the entire workflow and decision support algorithm in its full complexity in statistics software and keeping it in synchronization with future modifications of the server. Furthermore, the source code developed for the simulation is already available for implementation into the GlucoTab® system, in case of adopting algorithm modifications after the simulation. After additional reviews and testing, the code can be included in the medical device software.

Simulations are performed in two steps, with real patient data from the GlucoTab® clinical studies, **Figure 8**. In the first step, the simulator uses BG measurements and insulin dose calculations, as well as therapy adjustments, based on the original entries into the GlucoTab® system by the clinical personnel. Sequentially new insulin dose calculations are performed by using the new algorithm. In a second step BG estimations are performed. We identified several methods for BG estimations from a structured literature research (see section 3.1 – Structured literature search). Neural networks (NN) have been shown to be the most promising technologies [34], [35]. However, NN could not be used to achieve accurate BG estimations using our data. The GlucoTab® approach for T2DM does not involve exact carbohydrate counting. Therefore, exact amounts of carbohydrates consumed were not available and could account for the inaccurate estimations achieved with NN.

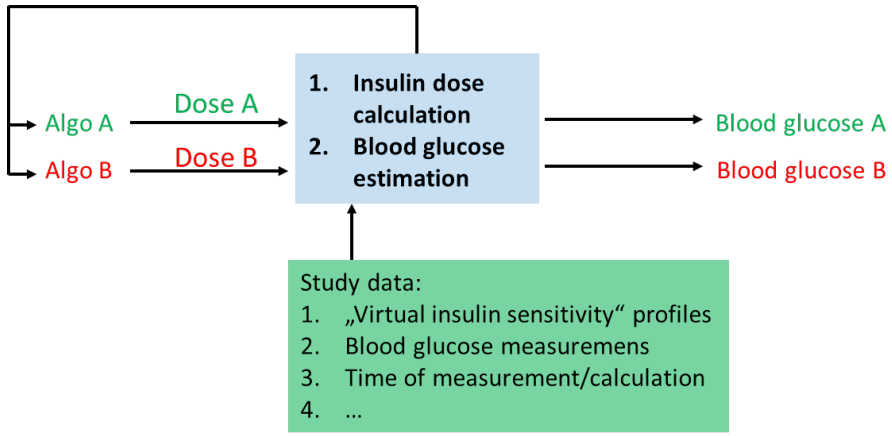

Figure 8: Steps performed in the workflow simulation for testing different versions of the insulin dosing algorithm

Thus we developed a new method for BG estimations in the toolbox by using “virtual insulin sensitivity” profiles. “Virtual insulin sensitivity” was defined as the difference between two BG measurements divided by the injected insulin dose. A "virtual insulin sensitivity" value is estimated for every measurement interval (e.g. noon to evening) for every patient on each hospital day. The simulator uses the “virtual insulin sensitivity” profile of the patients and calculates the estimated BG value for the next interval alongside the new insulin dose. An example of how BG estimations due to algorithm modifications are performed is illustrated in **Figure 9**.

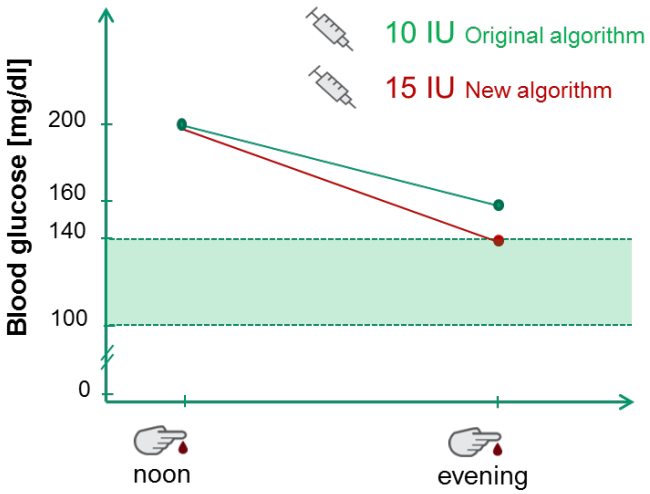

Figure 9: Example of blood glucose estimations due to algorithm modifications. IU ... Insulin Unit

A patient with a noon BG level of 200 mg/dL, an evening BG level of 160 mg/dL received 10 insulin units (IU) injected at noon, and thus has a “virtual insulin sensitivity” of 4 mg/dL/IU. In this example, one IU lowers the BG level by 4 mg/dL. In the simulation the patient receives 15 IU at noon, following the dose suggestion of the modified algorithm. Considering the “virtual insulin sensitivity” of the

patient, the simulation estimates that the additional 5 IU would have lowered the BG level by additional 20 mg/dl resulting in an evening BG level of 140 mg/dl.

All records resulting from the simulations are stored in the relational GlucoTab® database, and are then extracted by the data preparation component and prepared for pooled statistical analysis in the analysis component.

3. Blood glucose estimations

Parallel to the development of the toolbox suitable methods for the estimation/simulation of the effect of insulin dosing algorithm modifications on the patients' BG level were searched. Therefore a structured literature search was carried out in February 2013. The aim was to identify methods for BG estimation, which are: applicable in T2DM patients on intensified insulin therapy using subcutaneous insulin injections, for long-term BG estimations to the next meal, and which use input parameters also available in our data base. Identified methods were evaluated in terms of expectable results (accuracy), reliability and feasibility.

3.1 Structured literature search

Sources used:

- PubMed (National Center for Biotechnology Information)
- IEEE Xplore (Institute of Electrical and Electronics Engineers and Institution of Engineering and Technology)
- Google Scholar (Google Inc.)
- Google Web (Google Inc.)

Search strategy:

Initially, most recent review articles, PhD and master theses or books were searched. Based on the identified overview works, individual studies were identified and their abstracts were screened. Relevant sources were identified for critical appraisal. To identify also the most novel work a keyword search was performed. Again, abstracts were screened and relevant sources were included for critical appraisal.

Search results:

Two master theses, 3 PhD theses and one book chapter were initially identified. The identified overview work included state of the art analyses until 2012. 28 relevant published publications were selected for critical appraisal. The search results were categorized according to:

- Prediction algorithm/technology
- Diabetes type
- Glycemic source: CGM or capillary BG data
- Forecast period
- Method tested in a clinical trial
- Data base (subjects)

Twenty-one published new articles were identified meeting the keyword search criteria. For critical appraisal 10 new articles were additionally selected. The keyword queries and the critical appraisal are listed in Appendix III – Supplemental Material (Structured Literature Search: Critical Appraisal).

3.2 Identified methods for BG estimation

Models of glucose dynamics for predictive purposes can mainly be divided into two categories: *physiologically-oriented* models and *data-driven* methodologies. The latter category can furthermore be divided into time-series analysis using auto-regressive models and machine learning (ML) methodologies (e.g. neural networks (NN), support vector regression). Combinations of data-driven methods incorporating physiological sub-models present an additional approach.

Forecast period: The forecast period can be divided into three ranges according to the identified literature:

1. Short-term predictions (10 to 30 minutes)
2. Post-prandial predictions (30 to 120 minutes)
3. Long-term predictions(>120 minutes or to the next meal/interval)

Short-term predictions target especially online closed loop insulin systems using insulin pumps. Post-prandial and long-term predictions could also be used for basal-bolus insulin therapy.

Data input: The identified forecast methodologies significantly differ in the used input variables. The major difference is if glycemic monitoring was performed with a quasi-continuous data source (CGM)

or with point of care glucose testing, e.g. four times a day in case of a basal-bolus therapy. Additional information like consumed carbohydrates, physical activity, level of stress and relevant medications is often used in the predictive models.

3.2.1 Physiologically-oriented models

Previous work in this field dates back to the early 1960s. A historical background and summary of previous work can be found in Cescon (2011) and Stahl (2012) [36], [37]. Physiologically-oriented models are based on differential equations and are exclusively used for short-term glucose predictions. For example, a predictive capacity with a root mean square error (RMSE) of 4 mg/dL for a prediction horizon of 15 minutes was achieved [38]. The main advantages are that the models require no training and that their output is continuously explainable. But then, these models are only valid for T1DM and only achieve good prediction performance in short-term glucose predictions. No individualization of the used models is possible if they are not explainable with the model parameters. Therefore, physiologically-oriented models cannot "simply" be trained for different patients.

3.2.2 Data-driven methodologies

Glucose forecasting using data-driven methodologies is relatively new compared to physiologically-oriented methodologies. These technologies advanced in the late 1990s, similar to the development of the personal computer. Data-driven methodologies applied for glucose forecasting can be roughly divided into:

1. Time series analysis
    a. Regression (linear models and higher order polynomial models)
    b. Regression with learning components (exogenous inputs)
2. Machine learning methods
    a. Neural networks
    b. Support vector regression
    c. Gaussian processes

Gani et al. developed an auto-regressive (AR) model which is able to yield 30 minutes ahead glucose level predictions with a RMSE of 1.8 mg/dL and 60 min ahead glucose level predictions with a RMSE of 12.6 mg/dL [39]. One disadvantage using AR or auto-regressive moving average (ARMA) methods is that exogenous input, such as injected insulin or consumed carbohydrates does not influence the

prediction, which excludes them from being used in a model-based control framework. An extension to the AR concept is to include exogenous inputs, transforming these models into ARX or ARMAX models (X stands for exogenous input). In Percival et al. they demonstrated that a 3 hour look ahead with a RMSE of 26 mg/dL is possible using a multi-parametric model predictive control algorithm in virtual patients [40].

Neural networks (NN) are an additional option for glucose predictions. In Daskalaki et al. a NN model was compared to AR and ARX models on a dataset with 30 patients. The NN outperformed AR and ARX models in this study. The NN had a RMSE of 4.9 mg/dL versus 29 mg/dL (AR) and 26 mg/dL (ARX) for 45 minute glucose predictions. [41]

Long-term predictions with different NN topologies were performed in T1DM patients. In Quchani and Tahmai, the study aimed the prediction of the glucose concentration before lunch. The data were obtained from 10 T1DM patients treated with a conventional subcutaneous insulin regimen. The results showed that the Elman recurrent NN outperformed the multilayer perceptron network (mean absolute error 10.4 mg/dl vs. 24.15 mg/dl) [35]. Zainuddin et al. compared wavelet NN against other NN topologies. The system outperformed others for morning, noon, evening and night BG predictions with a RMSE < 0.04 mmol/L (<1 mg/dL) [34].

The biggest advantage, but the biggest disadvantage is that data-driven models can and have to be trained. Therefore no complex physiological model has to be developed to model the influence of parameters according to e.g. complex metabolic processes. The “nature” of these models is very patient-specific. However, the validity of the prediction is dependent on the quality of the training data (garbage in, garbage out problem). Furthermore, for exact predictions in the critical low-glycemic range the model has to be trained also with low BG values. Because low-glycemic events are rare, the training-dataset has to be very large.

3.3 Discussion

Reliable physiologically-oriented models for BG estimation are only available for short-term predictions in T1DM. Data-driven methodologies provide a broad array of options also for T2DM, but also primarily for short-term predictions. None of the identified methods for long-term predictions has been validated in clinical studies with T2DM patients. NN approaches using very detailed sets of data from T1DM showed very promising results [34]. Unfortunately, NN could not be used to achieve accurate BG estimations using our less detailed dataset of hospitalized T2DM patients. The GlucoTab®

approach for T2DM does not involve exact carbohydrate counting. Therefore, exact amounts of carbohydrates consumed were not available and could account for the inaccurate estimations achieved with NN. Patients were on average only for 8 days in the hospital in our studies testing the insulin dosing algorithms. By having only this short period of time available, the development and test of a patient-specific NN was problematic. Additionally, the development of a generic NN model using a pooled data source would probably not sufficiently take into account intra- and inter-personal variations and should therefore not be used for BG estimations.

Because of the lack of suitable methods for long-term BG level estimation in T2DM patients by using our data source, a rather simple but explainable and reliable method was developed – "virtual insulin sensitivity" profiles. For analyses of the impact of possible modifications of the insulin dosing algorithm on the patients' BG levels a linear relationship between the magnitude of the insulin dose and the effect on BG levels was used [42]. Most bolus insulin calculators work according to this principle. By using this approach also unreported events, e.g. unreported snacks and stress are automatically considered in the retrospective what-if estimation of the potential impact on the patients' individual BG level. Like in Zainuddin et al. "estimators" were developed for individual intervals (bedtime to morning, morning to noon, noon to evening, evening to bedtime) [34].

The accuracy of the BG estimation method using "virtual insulin sensitivity" profiles may be limited by the non-linearity of the BG lowering effect of insulin across the patients' BG range. In the normoglycemic range insulin sensitivity can be considered as a constant [43], [44], but the BG lowering effect may be amplified in hypoglycemia and dampened in hyperglycemia. In a clamp study performed in T1DM patients the BG lowering effect increased by 75% when BG dropped from 90 to 50 mg/dL and decreased by 10% when BG was increased from 100 to 200 mg/dL [45]. However, no data is available to support these findings in T2DM patients. The vast majority of simulations were performed with BG levels in a range were the BG lowering effect of insulin can be considered as linear. Therefore, the validation of the BG estimations was demonstrating a good agreement between simulation and clinical data, (Chapter III). Future versions of the BG estimation component could use non-linearity of the insulin lowering effect, providing reliable data for T2DM are available.

4. Summary

Especially for comparison with other studies already established parameters and metrics for the evaluation of the level of glycemic control have been identified, and were incorporated into the analysis component of the toolbox as reusable methods. Furthermore, newly developed methods, measures and metrics provide detailed insight into individual and pooled analyses of the level of glycemic control and allow the evaluation of safety and effectiveness of insulin dosing algorithms.

In the course of this PhD work a framework/toolbox was developed incorporating methods for: 1) data preparation of heterogeneous data sources from clinical studies; 2) analysis and evaluation of the performance of insulin dosing algorithms; and 3) simulation and estimation of the impact of modifications of insulin dosing algorithms. The toolbox currently comprises data of 258 patients. 92 additional patients have been included into the database since the publication of Donsa et al. 2014 [23]. Furthermore, new methods for reporting of analyses and simulation have been developed and the reporting tool was changed from Sweave/LaTeX to Markdown. By using Markdown it is now possible to create reports in different file formats, including PDF, Microsoft Word and HTML. Markdown as the newer technology facilitates the development of interactive documents and graphs.

The use of "virtual insulin sensitivity" profiles allows simple but explainable and reliable estimations of BG levels. In combination with the workflow simulator it is possible to investigate modifications of insulin dosing algorithms "in-silico" prior to testing them in a clinical study. Chapter III provides validations of simulation results using clinical data of patients treated with modified versions of the insulin dosing algorithm.

Also in repeatedly performing the literature keyword search to identify the most novel methods for BG estimation, no studies were identified testing long-term BG estimation methodologies in a clinical study in T2DM patients. However, the main focus of this work was not the estimation of BG levels, but the evaluation and improvement of an insulin dosing algorithm. For the purpose of estimating the impact of modifications of the insulin dosing algorithm on the patients' BG levels the used method proofed to be sufficient.

CHAPTER III

Evaluating modifications of the insulin dosing algorithm

This chapter is based on data and analyses of previously published articles (**Donsa** et al. 2014; Schaupp*, **Donsa*** et al. 2015; Neubauer, Mader, Höll, Aberer, **Donsa** et al. 2015) and is complemented by so far unpublished investigations.

Methods for data processing and statistics are described in detail in the original articles.

* Both authors contributed equally to this study.

1. Evaluation of the initial version of the insulin dosing algorithm – Room for improvement

The initial version of the insulin dosing algorithm used in GlucoTab® was tested in a proof-of-concept study using a paper-based protocol for basal-bolus insulin therapy [22]. Seventy-four T2DM patients were either assigned to algorithm-based treatment with a basal-bolus insulin therapy or to standard glycemic management. The following investigations were performed with data from 37 T2DM patients on algorithm-based diabetes therapy. Detailed clinical characteristics on admission, preexisting diabetes therapy and admission diagnosis are provided in the originally published study [22].

Glycemic control:

The percentage of BG values in the target range (100 – 140 mg/dL) was significantly higher in the algorithm group compared to the standard glycemic management group (34% vs. 23%, $p<0.001$) [22]. The number of BG readings in the desired range 100 – 140 mg/dL increased during the progression of the therapy in the algorithm group, (**Figure 5**, Chapter II). In the course of the therapy, the mean daily BG levels in the algorithm group were significantly reduced from 204±65 mg/dL (baseline) to 148±32 mg/dL (last 24h), $p<0.001$. But 30% of the patients in the algorithm group had at least one low glycemic event (<70 mg/dL) which indicated room for improvement to establish a safer and more effective glucose management.

More detailed analysis of the patient's glycaemia, including additional CGM data, revealed on average high BG levels at noon and an increased number of low glycemic events (<70 mg/dL) in the afternoon, **Figure 10**. CGM profiles were stable during night, but glucose levels at noon were frequently outside the target range. This was presumably caused by an elevated morning BG excursion which was not satisfactorily controlled by the administered morning bolus insulin dose. Also a rise of BG levels in the early morning hours (4:00 - 7:00) indicated an additional insulin need in the patients treated with the basal-bolus insulin regimen. To fit into the workflow of the clinical ward, basal insulin was administered at noon and therefore fading basal insulin action in the morning could also have contributed to elevated BG levels at noon [46]. As a consequence elevated BG values at lunch required higher bolus insulin doses and could have caused hypoglycemia in the afternoon [22]. Although there are hurdles regarding CGM accuracy which are discussed in Chapter IV [47], CGM data provided information that would not have been recognized by only using capillary BG measurements.

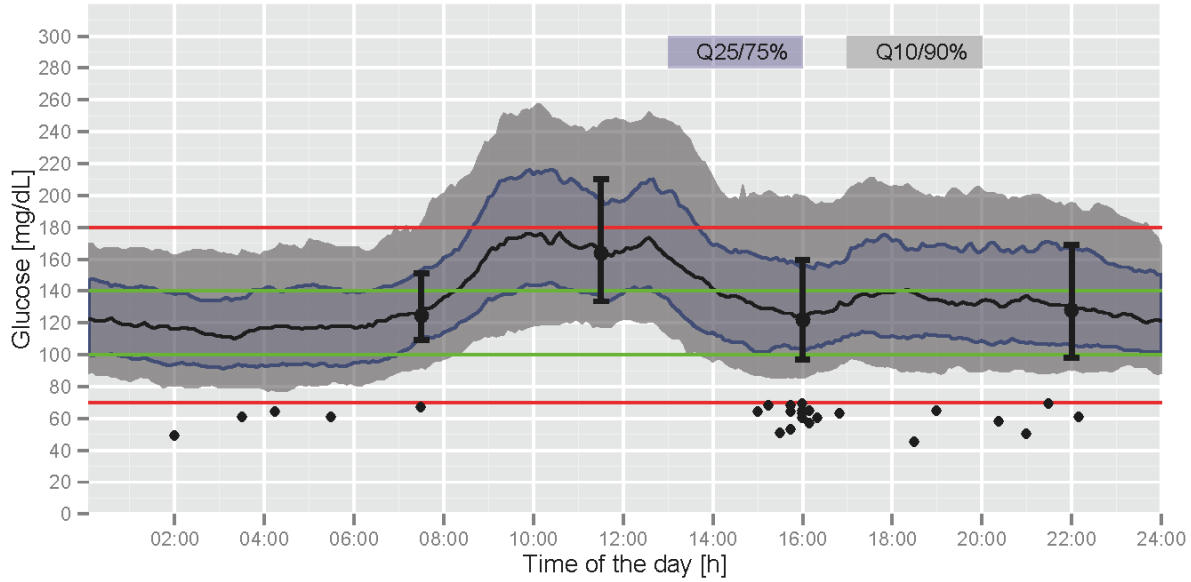

Figure 10: Diurnal glycemic profile of patients treated with the initial version of the insulin dosing algorithm. CGM values are median – interquartile range (25–75% [Q25/75%] and 10–90% [Q10/90%]). BG values are median – interquartile range (25–75%), displayed as bars. Black dots indicate hypoglycemic events (<70 mg/dL). Q …quantile, h … hour

Basal-bolus insulin therapy:

The basal-bolus insulin regimen in T2DM patients targets a 50:50 ratio of basal and bolus insulin. **Figure 11** shows the development of the basal and bolus insulin as a function of treatment days. Especially in the first days of therapy some patients required significant amounts of supplemental insulin to account for high BG values disregarding this 50:50 ratio, **Figure 11a**. On the first day the displayed average amount of bolus insulin is lower because patients were enrolled at different times of the day and did not receive all 3 planned bolus insulin injections. By investigating the diurnal bolus insulin distribution a proportional higher supplemental insulin requirement at noon was discovered, **Figure 11b**. Sixty-four percent of mealtime bolus insulin doses were adjusted for too high or too low BG values, and the majority of positive corrections of bolus insulin doses were performed at noon. Only 11% of bolus doses at noon were reduced in the patient cohort. A negative correction is, if the mealtime bolus insulin dose is reduced by 50% when the patients' BG level is between 70 and 100 mg/dL, or if the bolus is withheld when the BG level is below 70 mg/dL.

Also a detailed investigation of "correction patterns" revealed that a large proportion of bolus insulin calculations were supplemented by additional corrective insulin, **Table 1**. This indicated that some patients required more insulin than the algorithm initially provided to account for high BG levels. Furthermore, although some patients were constantly in the need of supplemental bolus insulin

compensating high BG levels, the patient's TDD was not increased by the insulin dosing algorithm due to morning and evening BG values slightly below 100 mg/dL, **Table 2**. In 14% (29 of 204) of "therapy patterns" the TDD was increased two times in a row, but in only 18% (42 of 235) of all therapy adjustments the TDD was decreased.

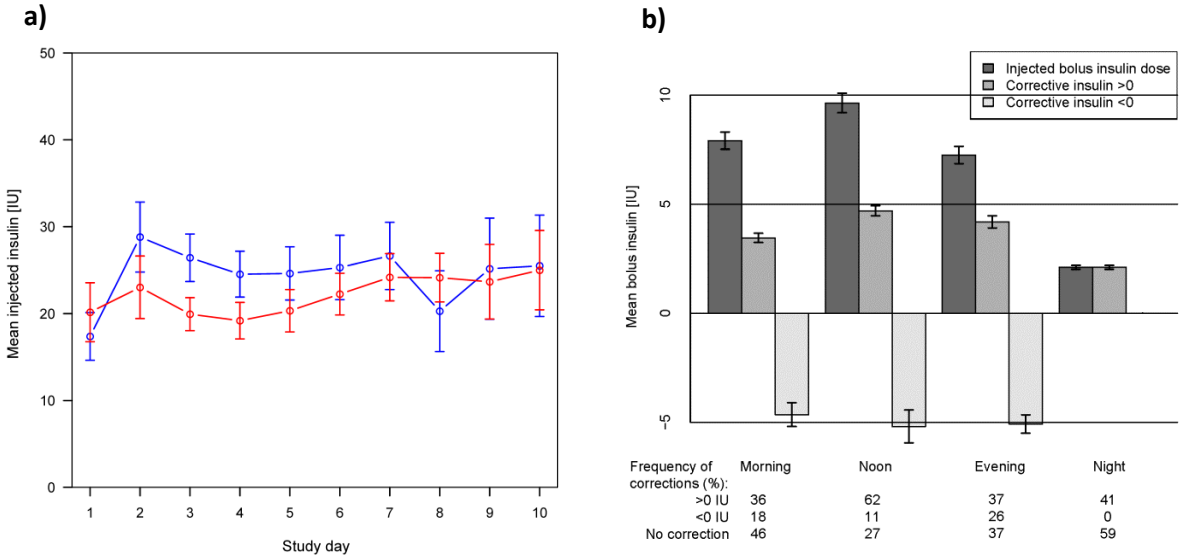

Figure 11: a) Composition of the injected insulin. Mean injected bolus insulin (blue) and mean injected basal insulin (red) as a function of study days. **b)** Composition of the bolus insulin and frequency of bolus corrections over the day. The error bars are the standard error of the mean

Table 1: Correction pattern histogram (top 10): Sequence of adjustments of bolus insulin doses to compensate for high and low BG levels in patients treated with the initial version of the insulin dosing algorithm. (+) indicates additional corrective insulin; (-) indicates a decrease of the bolus dose suggestion; (0) indicates no bolus adjustment. In total 235 correction patterns and 59 unique patterns

Correction pattern	Correction bolus				Frequency	
	1. Noon	**2.** Evening	**3.** Night	**4.** Morning	n	%
++++	+	+	+	+	27	11.5
+000	+	0	0	0	18	7.7
++00	+	+	0	0	13	5.5
++0+	+	+	0	+	12	5.1
+-00	+	-	0	0	11	4.7
+0++	+	0	+	+	11	4.7
+-0-	+	-	0	-	10	4.3
0000	0	0	0	0	10	4.3
+0+0	+	0	+	0	8	3.4
+00+	+	0	0	+	8	3.4

Table 2: Therapy pattern histogram (top 10): Sequence of adjustments of mealtime bolus insulin doses and adjustments of the patients' TDD to compensate for high and low BG levels in patients treated with the initial version of the insulin dosing algorithm. (+) indicates additional corrective insulin; (-) indicates decrease of bolus dose suggestion; (0) indicates no bolus adjustment; (n) indicates a missed insulin injection; (UP) indicates a TDD increase; (==) indicates no adjustment of the TDD; (DW) indicates a decrease of the TDD. In total 204 therapy patterns and 83 unique patterns

Correction pattern	0. TDD adjustment	Correction bolus			4. next TDD adjustment	Frequency	
		1. Noon	2. Evening	3. Morning		n	%
UP+++UP	UP	+	+	+	UP	17	8.3
==+++UP	==	+	+	+	UP	13	6.4
==+00==	==	+	0	0	==	12	5.9
==+-0==	==	+	-	0	==	10	4.9
==000==	==	0	0	0	==	10	4.9
==+--DW	==	+	-	-	DW	7	3.4
==++0==	==	+	+	0	==	6	2.9
==00-==	==	0	0	-	==	6	2.9
==+0+==	==	+	0	+	==	5	2.5
==n++UP	==	n	+	+	UP	5	2.5

2. Evaluating the impact of modifications of the insulin dosing algorithm

After the initial evaluation of the first version of the insulin dosing algorithm different approaches for improvement were identified, simulated and evaluated. This section provides an overview of the sequence of implemented algorithm improvements and provides evaluations based on simulations and validations with real patient data. Finally, a comparison regarding safety and effectiveness of the initial insulin dosing algorithm with the currently used version was performed.

2.1 Redistribution of daily bolus insulin

The use of the first version of the insulin dosing algorithm resulted in frequent relatively high BG values at noon, requiring significantly more corrective bolus insulin which resulted in an increased number of hypoglycemic episodes in the afternoon. The first step for improving the insulin dosing algorithm was to redistribute the amount of bolus insulin over the day. Originally, each meal (breakfast, lunch and dinner) was accounted for with an equally large bolus insulin dose in relation to the patients' TDD. Because of high BG levels at noon the idea was to increase the morning bolus insulin dose to account for additional insulin need. For safety reasons the TDD was not increased and therefore the amount of insulin was reduced for the other two boluses. The in Chapter II described framework for workflow simulation was used to estimate the effect of redistributing daily bolus insulin

on the patients' BG levels. Therefore several combinations of redistributing the daily bolus insulin were simulated and patient hazard was investigated by using what-if analyses. The amount of bolus insulin at noon was reduced to lower the risk of potentially dangerous insulin stacking leading to hypoglycemia in the afternoon. The final distribution of bolus insulin over the day resulted in 45% for breakfast, 25% for lunch and 30% for dinner of half of the patients' TDD, and the other half was still administered as basal insulin at noon. Workflow simulations with BG estimations were indicating no additional BG levels below 70 mg/dL by redistributing daily bolus insulin accordingly.

Figure 12a shows the initial problem of high BG levels at noon in data of 52 patients treated with the initial version of the insulin dosing algorithm. **Figure 12b** demonstrates the results of the simulation with the proposed change of the daily bolus insulin distribution. The simulation predicted a reduction of BG levels at noon without causing additional hypoglycemia. Results of the simulation were validated using data of the first 15 patients treated in a clinical study with the redistributed daily bolus insulin, **Figure 12c**. In these patients the predicted significantly reduced noon BG levels were confirmed, p=0.014. [23]

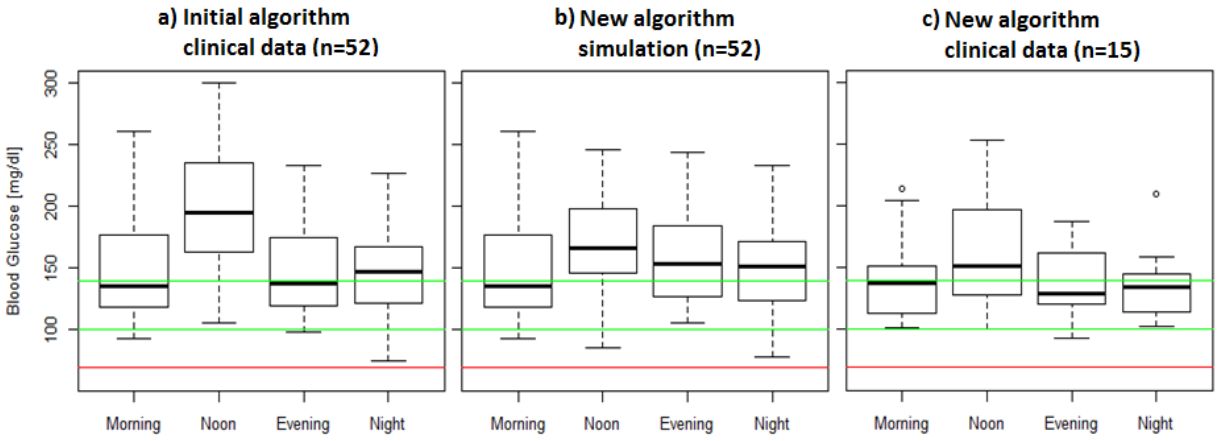

Figure 12: Diurnal distribution of average blood glucose levels per hospital stay – clinical data and simulation results. Data from Donsa et al. 2014 [23]

2.2 Modification of the TDD adjustment (therapy adjustment)

In some patients the need for insulin was noticeable higher than initially calculated at the start of the therapy, and moreover the adjustment of the therapy was not dynamic enough to adjust the TDD to the required amount of insulin during the patients' short hospital stay. The therapy pattern analysis of

the initial insulin dosing algorithm revealed that in some patients, therapy adjustments resulted in no increase of the TDD even though they became significant amounts of supplemental insulin. The additional supplemental insulin requirement compensating high BG levels is not considered in the adjustment of the TDD for safety reasons. To make the method for adjusting the TDD more dynamic without compromising safety, different versions were simulated by using the framework for workflow simulation described in Chapter II. Consequently, patient hazard analyses were performed to identify safe and effective modifications.

Description of potential new versions for adjustment of the TDD:

- Version 1 (V1): In addition to the initial therapy adjustment scheme (see **Table 3**), the TDD is increased when the morning and evening BG values are >100 mg/dL and additionally the mean/median BG value of all four standard measurements is >140 mg/dL, **Table 3**
- Version 2 (V2): In addition to the initial therapy adjustment scheme, the TDD is increased when the morning and evening BG values are >70 mg/dL and additionally the mean/median BG value of all four standard measurements is >140 mg/dL, **Table 4**
- Version 3 (V3): In addition to the initial therapy adjustment scheme, the TDD is increased when all four standard BG measurement values are >100 mg/dL and additionally the mean/median BG value of all four standard measurements is >140 mg/dL, **Table 3**

Table 3: Adjustment of the TDD (initial, version 1 and version 3): Initially the adjustment of the TDD was based on morning and evening BG values and considered if the patient had any BG value <70 mg/dL. Version 1 of the proposed new methods for TDD adjustment would increase additionally the TDD by 10% in the green marked fields in the table if the mean/median of all 4 standard BG measurements is >140 mg/dL. Version 3 requires all 4 available BG standard measurements >100 mg/dL and the mean/median >140 mg/dL to increase the TDD. The availability of morning and evening BG measurements is obligatory for adjustment of the TDD

		Morning					
	Range (mg/dL):	**<70**	**70 – 100**	**101 – 140**	**141 – 180**	**>180**	**Round down new total daily dose**
Evening	**<70**	-20 %	-20 %	-20 %	-20 %	-20 %	
	70 – 100	-20 %	-10 %	± 0 %	± 0 %	± 0 %	
	101 – 140	-20 %	± 0 %	±0%/+10%	±0%/+10%	+ 10 %	
	141 – 180	-20 %	± 0 %	±0%/+10%	+ 10 %	+ 10 %	
	>180	-20 %	± 0 %	+ 10 %	+ 10 %	+ 20 %	

Table 4: Adjustment of the TDD (version 2): The proposed new method for TDD adjustment would increase additionally the TDD by 10% in the green marked fields in the table if the mean/median of all 4 available standard BG measurements is >140 mg/dL. The availability of morning and evening BG measurements is obligatory for adjustment of the TDD

		Morning					
	Range (mg/dL):	**<70**	**70 – 100**	**101 – 140**	**141 – 180**	**>180**	**Round down new total daily dose**
Evening	**<70**	-20 %	-20 %	-20 %	-20 %	-20 %	
	70 – 100	-20 %	-10 %	±0%/+10%	±0%/+10%	±0%/+10%	
	101 – 140	-20 %	±0%/+10%	±0%/+10%	±0%/+10%	+ 10 %	
	141 – 180	-20 %	±0%/+10%	±0%/+10%	+ 10 %	+ 10 %	
	>180	-20 %	±0%/+10%	+ 10 %	+ 10 %	+ 20 %	

To determine the effect of modifications of the above described versions for adjustment of the patients' TDD, workflow simulations were performed with data from the initial pilot study (37 patients, 235 adjustments of the TDD). **Table 5** shows a summary of the frequency of the TDD adjustments based on initial and recalculated modified versions.

Table 5: Recalculations of the TDD based on different versions for adjustment of the TDD. The numbers indicate the frequency of TDD adjustments and the sign and number implies the increase/decrease and percentage of change of the TDD. (+10%n) are dose adjustments according to the new rules

Type	Initial TDD adjustment	TDD adjustment (new)					
		V1 Mean	V1 Median	V2 Mean	V2 Median	V3 Mean	V3 Median
+-0%	118	81	88	75	83	84	90
+10%	60	60	60	60	60	60	60
+10%n	0	37	30	43	35	34	28
+20%	15	15	15	15	15	15	15
-10%	13	13	13	13	13	13	13
-20%	29	29	29	29	29	29	29

Potential patient hazard (hypoglycemia) was analyzed to evaluate the safety of the new versions for adjustment of the TDD. Therefore, if a TDD prior to a hypoglycemic event would have been increased was investigated. Additionally, the impact of increased insulin as calculated by the new version of TDD adjustment was investigated, and the in Chapter II described BG estimation methodology was used to identify potential additional hypoglycemia.

Four cases were identified where the new versions for adjustment of the TDD would increase the insulin dose prior to a hypoglycemic event, **Table 6**. The impact of increased doses on hypoglycemia and the impact of modified rules for adjustment of the TDD on insulin dose calculations are shown in **Table 7**. Only few BG values were influenced by additional 10% of daily insulin and lowering the BG levels below 70 mg/dL. The average change of the TDD was small and comparable between the different versions. The maximum of additional insulin was lower in version 3 compared to the other versions. It has also to be considered that the 10% increase of the TDD is not a single insulin injection, but is divided into a basal and a bolus part, and the bolus part is furthermore divided into 3 meal boluses. Therefore, the amount of additional insulin is relatively small. In most cases the basal dose would only be increased by 1-2 IU and the bolus accordingly.

According to this analysis, version 3 (mean) of the proposed new methodologies for adjustment of the patients TDD was implemented into the final version of GlucoTab®. Analyses and simulations confirmed that it is safe and it is more dynamic compared to the initial methodology. By considering all 4 BG measurements and their mean, this method is increasing in complexity and therefore it is only advisable to use this method in a computerized system to prevent user calculation errors.

Table 6: Increased TDD adjustments prior to hypoglycemic events. The numbers demonstrate the amount of insulin for the initially calculated TDD and the recalculation with the proposed modified versions. The bottom row indicates how many calculations were deviating from the original TDD calculation

Subject ID	TDD initial	V1 mean	V1 median	V2 mean	V2 median	V3 mean	V3 median
	Insulin Units (IU)						
119	22	24	22	24	22	22	22
135	46	50	50	50	50	50	50
135	36	39	39	39	39	39	39
136	46	46	46	50	50	46	46
		3/4	2/4	4/4	3/4	2/4	2/4

Table 7: Effect of the modified adjustment of the TDD on hypoglycemia and calculation of insulin doses. The average difference between originally calculated and recalculated TDD is demonstrated as mean±SD and as median and range. Impact of increased doses on hypoglycemia (<70 mg/dL) was investigated by using the BG estimation process described in Chapter II

Version	Events <70 mg/dL	Mean±SD	Median	Range
	n	Insulin Units (IU)		
Original	31	–	–	–
V1 mean	32	4.3±2.3	4	1 – 11
V1 median	31	4.6±2.1	4	1 – 11
V2 mean	34	4.3±2.4	4	1 – 11
V2 median	33	4.6±2.4	4	1 – 11
V3 mean	31	4.2±1.9	4	1 – 7
V3 median	31	4.6±1.6	4	1 – 7

2.3 Safety features

Insulin on board:

Insulin on board is a safety feature used in modern bolus insulin calculators to protect DM patients from potentially dangerous insulin stacking. Basal-bolus insulin therapy allows flexibility by frequent injections of small precise doses at any time that a need arises. As a consequence, this may result in an overlap of insulin action times. In determining how much insulin from earlier boluses is still "active", the calculation of subsequent bolus insulin calculations is influenced. The still remaining "active" insulin is estimated and subtracted from the current bolus calculation according to the pharmacodynamics of the used insulin. In many cases a linear relationship for insulin on board over time is used. [42], [48]

The use of computerized workflow and decision support systems allow the handling of time-critical calculations such as the reduction of bolus insulin due to still "active" insulin on board. GlucoTab® automatically subtracts still "active" insulin when calculating a new bolus insulin dose.

In a post-hoc analysis using data from Neubauer et al. [30] the frequency of bolus reduction due to insulin on board was investigated. Even in a highly standardized environment under study conditions 18.8% of bolus insulin calculations were reduced by at least one IU due to the insulin on board safety feature. The average reduced bolus insulin dose was 3.2±3.0 IU (mean±SD).

Reduced insulin for belated basal insulin administration:

The GlucoTab® approach for basal-bolus insulin therapy in T2DM patients requires basal insulin administration at noon. Because of patients enrolling to therapy e.g. in the afternoon, or workflow deviations due to larger medical procedures it is sometimes necessary to administer basal insulin belated. GlucoTab® supports automated handling of belated basal insulin administration by reducing the amount of insulin according to a formula.

2.4 Comparison of the initial with the refined insulin dosing algorithm

Both versions of the insulin dosing algorithm were tested in clinical studies and have been thoroughly evaluated [22], [30]. The initial dosing algorithm was tested in a paper-based way in a pilot study. Results regarding efficacy and usability were published by Mader et al. 2014 [22] and additionally so far unpublished investigations have been presented in the previous sections of this PhD thesis.

After integration of the redistribution of daily bolus insulin, modification of the method for daily insulin dose adjustment and implementation of safety features, the refined insulin dosing algorithm was tested in a computerized way on 4 hospital wards [30]. Results of this study regarding safety, efficacy and usability can be found in Chapter V.

The aim of this section is to compare the already published results of both versions of the insulin dosing algorithm and to complement analyses by so far unpublished data. Originally published results are clearly marked. The patient population did not differ in any relevant parameters between patients treated with the initial and the refined version of the insulin dosing algorithm.

Glycemic control:

Overall glycemic control was comparable between the groups, **Table 8**. As the simulation predicted (section 2.1, [23]), the redistribution of the daily bolus insulin resulted in significantly lower BG levels at noon. The use of the refined algorithm did not increase hypo- or hyperglycemia. There is a trend towards a reduction of hypoglycemia when using the refined algorithm. This may have two different, but unfortunately inseparable explanations: Insulin dosing errors due to manual insulin dose calculation have a strong influence on the likelihood to experience hypoglycemia ([6], Chapter VI). As the refined computerized algorithm prohibits manual dose calculation errors, the rate of hypoglycemia may be reduced in this group. Additionally, the refined algorithm with redistributed daily bolus insulin

and safety features may have prevented hypoglycemia. Unfortunately, it is not possible to measure one effect without the other and the impact cannot be considered separately.

Table 8: Glycemic control established with the original and the refined algorithm. The rate of values <70 mg/dL of the initial algorithm was published in Mader et al. 2014 [22] and the glycemic profile of the refined algorithm was published in Neubauer et al. 2015 [30]

Profile	Initial algorithm	Refined algorithm	p-value
Patients (n)	37	99	
Mean daily BG and SD (mg/dL)	155±46	154±35	0.475
Mean prebreakfast	138±21	147±43	0.861
Mean prelunch	190±40	170±54	0.014*
Mean predinner	147±41	153±39	0.805
Mean bedtime	144±37	153±39	0.932
<70 mg/dL (%)	3.0	1.9	>0.2
70-180 mg/dL (%)	72.9	72.5	
100-140 mg/dL (%)	32.5	33.0	
>180 mg/dL (%)	23.5	25.6	

***statistically significant difference (p<0.05)**

In a subgroup of patients additional CGM was performed. CGM data processing is described in Chapter IV [47]. By using CGM data the diurnal distribution of glucose levels on the last treatment day was investigated and compared between patients treated with the initial and refined insulin dosing algorithm, **Table 9** and **Figure 13**. In patients treated with the refined version of the insulin dosing algorithm a reduction of the patients' mean daily glucose on the last treatment day was observed (CGM: 145.1±37.3 mg/dL vs. 132.6±34.0 mg/dL, p=0.081). The refined algorithm led to less glucose values in the range >180 mg/dL and an increase of glucose values in the extended target range 70 – 180 mg/dL.

Using only information from capillary BG measurements for comparisons would detect a higher proportion of BG values <70 mg/dL in patients treated with the refined insulin dosing algorithm on the last day of treatment. The detected low glycemic events (<70 mg/dL) were all during nighttime. A previous study demonstrated that during nighttime the number of low glycemic events detected by CGM was 15-fold higher than the number detected with capillary BG measurements [47]. By using additional information from CGM the rate of low glycemic events on the last day of treatment was comparable between patients treated with the initial and the refined version of the insulin dosing algorithm.

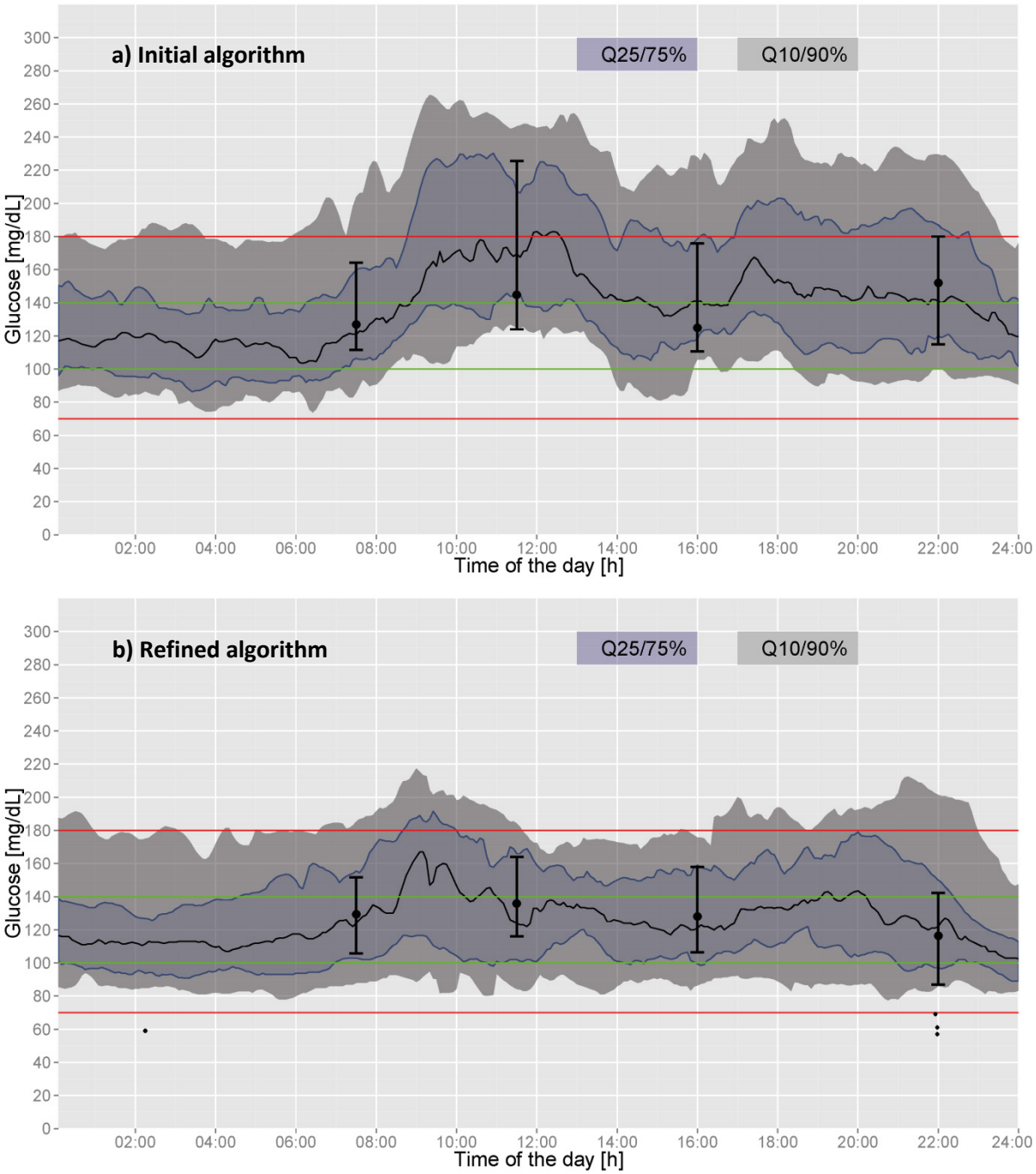

Figure 13: Last full treatment day with continuous glucose monitoring (CGM): **a)** Initial algorithm **b)** refined algorithm. CGM profiles and reference blood glucose (BG) measurements. CGM values are median – interquartile range (25–75% [Q25/75%] and 10–90% [Q10/90%]). BG values are median – interquartile range (25–75%), displayed as bars. Small black dots indicate hypoglycemic events (<70 mg/dL). Q …quantile, h … hour

Table 9: Ambulatory glucose profile of patients on the last study day under basal-bolus insulin therapy. Comparison between continuous glucose monitoring (CGM) and capillary blood glucose (BG) measurements for patients treated with the initial and refined insulin dosing algorithm. Data from Schaupp, Donsa et al. 2015 [47].

Profile	Initial algorithm		Refined algorithm	
	CGM	BG	CGM	BG
Patients (n)	28	28	35	35
Glucose values (n)	7,601	100	9,846	140
Mean daily glucose (mg/dL)	145.1	149.0	132.6	143.9
Glucose variability SD (mg/dL)	37.3	40.6	34.0	64.5
Coefficient of variation CV (%)	25.7	27.2	25.6	44.8
<50 mg/dL (%)	1.18	0.00	0.02	0.00
<60 mg/dL (%)	1.66	0.00	0.56	1.43
<70 mg/dL (%)	2.62	0.00	3.31	2.86
70-180 mg/dL (%)	74.92	78.00	82.96	84.29
100-140 mg/dL (%)	39.65	39.00	40.84	36.43
>180 mg/dL (%)	22.46	22.00	13.73	12.86
>250 mg/dL (%)	4.41	5.00	1.98	1.43
>350 mg/dL (%)	0.16	1.00	0.24	0.71

Basal-bolus insulin therapy:

The progression of the patients' starting bolus and basal insulin over the study period was significantly different between patients' treated with the initial and refined version of the insulin dosing algorithm, **Figure 14a**. The investigation of the progression of the TDD over the study period by including an interaction relationship with the used version of the insulin dosing algorithm in a linear regression model confirmed these differences, $p<0.05$. The refined version of the insulin dosing algorithm constantly increased the average TDD compared to patients treated with the initial version, **Figure 14b**. This is probably due to the new more dynamic methodology for adjustment of the TDD described in section 2.2.

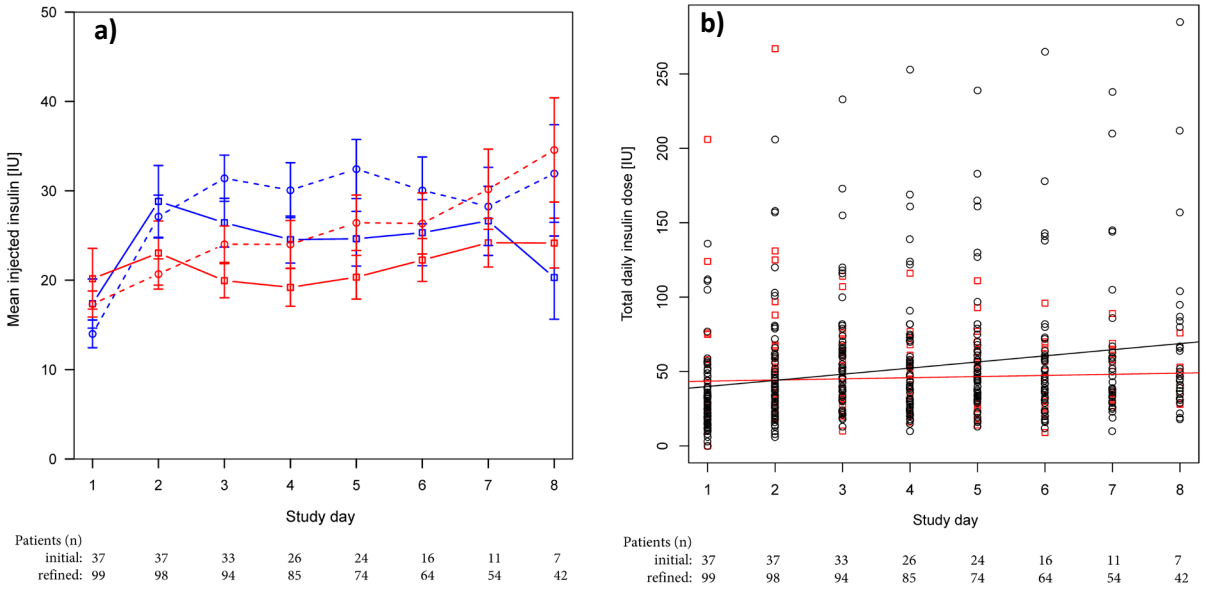

Figure 14: a) Progression of basal (red) and bolus (blue) insulin in patients using the initial (squares and solid lines) and the refined (circles and dashed lines) insulin dosing algorithm. **b)** Progression of the total daily insulin dose and linear regression line of patients treated with the initial (red squares) and refined (black circles) algorithm.

Evaluation of safety and effectiveness of the insulin dosing algorithms:

Individual decision support steps of the insulin dosing algorithms were evaluated using the method described in Chapter II (section 1.2). The initial problem of high BG levels at noon and the increased number of hypoglycemic events in the afternoon is also evident in **Figure 15a**. However, already a high proportion of calculated insulin doses resulted in BG levels in the extended target range (ETR) using the initial insulin dosing algorithm. Additionally, the impact of algorithm modifications is observable, **Figure 15b**. There are proportionally fewer dosing decisions resulting in hypoglycemia using the refined algorithm, especially in the noon-evening interval. The increased bolus insulin dose in the morning resulted in a better control of noon BG values, **Figure 16**. A small number of BG values in the hypo- and hyperglycemic range limit the interpretation of the average correctness of BG level "titrations" with supplemental insulin.

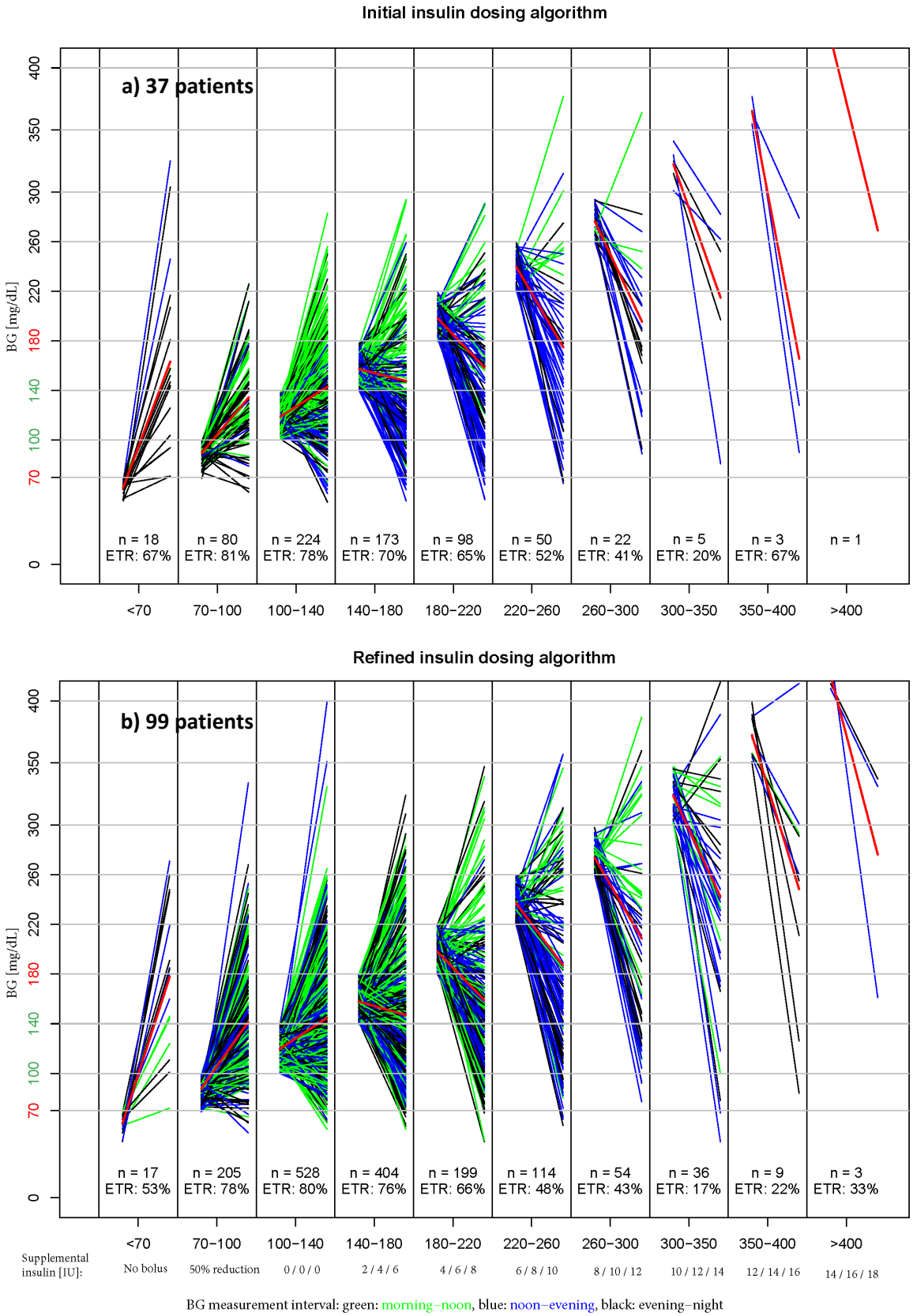

Figure 15: Target range approach: Evaluation of safety and effectiveness of the initial **(a)** and the refined **(b)** insulin dosing algorithm: The red line is the mean of all lines within an intervention border. Supplemental insulin dose according to blood glucose intervention border (mg/dL) and insulin sensitivity [sensitive / normal / resistant]; IU … Insulin Unit, ETR … Extended Target Range (70-180 mg/dL)

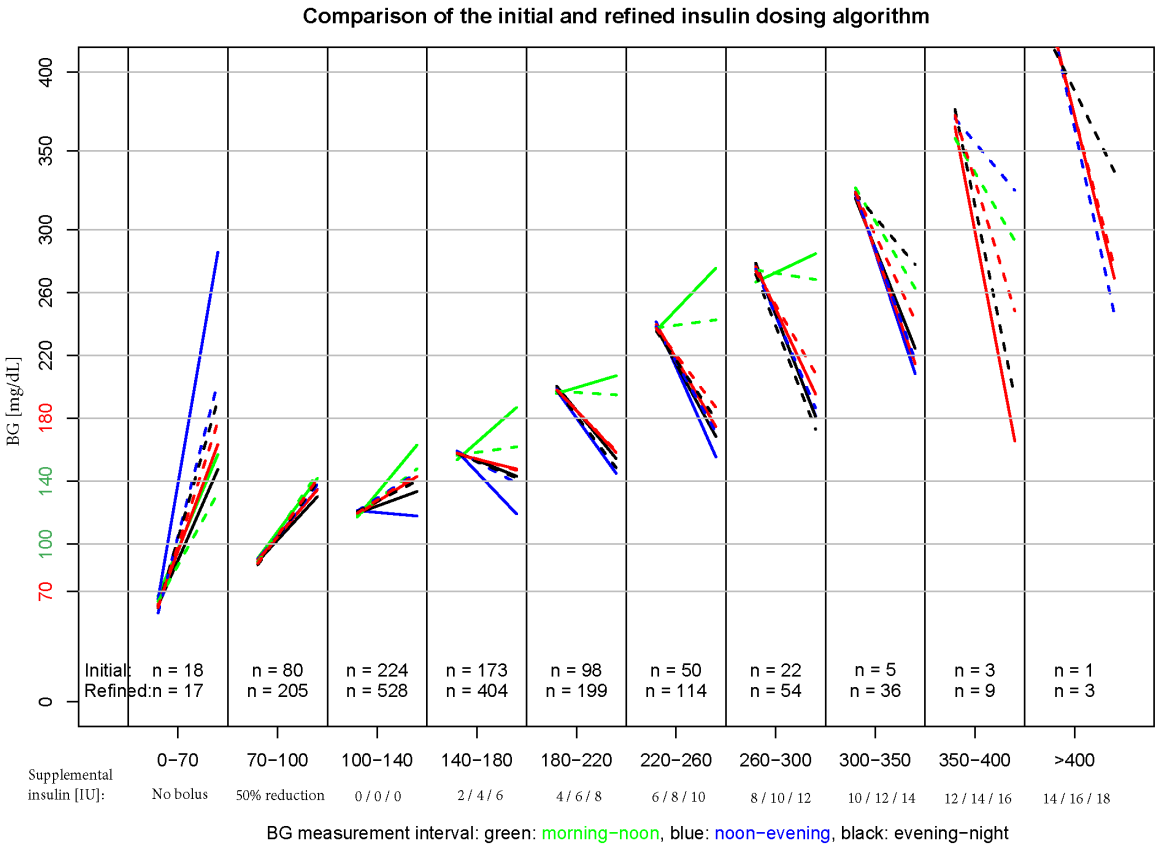

Figure 16: Average correctness of BG level "titrations" with supplemental insulin. Initial insulin dosing algorithm (solid lines) and refined insulin dosing algorithm (dashed lines). The red line is the mean of all lines within an intervention border. Numbers indicate the amount of underlying data for calculation of the averages. Supplemental insulin dose according to blood glucose intervention border (mg/dL) and insulin sensitivity [sensitive / normal / resistant]; IU … Insulin Unit

3. Summary

Evaluations of the already implemented modifications of the insulin dosing algorithm confirmed their safety and effectiveness. Moreover, the results of the "in-silico" simulations of modifications of the insulin dosing algorithm were confirmed with clinical data. Results of the "in-silico" simulation of the redistribution of the daily bolus insulin were validated using clinical data of the first 15 patients treated in a clinical study with the redistributed daily bolus insulin, but might have also been affected by the difference in glycemic control prior to the clinical study [23]. HbA1c in patients treated with the initial version of the insulin dosing algorithm was 76±30 mmol/mol compared to 62±18 mmol/mol in patients treated with the modified version. However, the amount of the by the simulation predicted BG reduction was once more confirmed in 42 patients on an Endocrinology ward with on average

poor glycemic control prior to the study (HbA1c: 70±24 mmol/mol) [30]. Modification of the methodology for adjustment of the patients TDD significantly changed the overall progression of the amount of daily injected insulin. Despite on average more ordered insulin due to the modified more dynamic adjustment of the TDD, no additional hypoglycemia was caused when compared to the initial insulin dosing algorithm. Glycemic control on the last study day was improved by using the refined insulin dosing algorithm. The patients' mean daily BG level was lower and the percentage of high BG levels was reduced compared to patients treated with the initial insulin dosing algorithm. Furthermore, the insulin on board safety feature in GlucoTab® reduced 18.8% of bolus insulin calculations which highlights the need for more elaborate workflow and decision support even under study conditions.

The comparisons of diabetes management were performed in best practice clinical studies. Both, the initial and the refined insulin dosing algorithm showed at least similar BG control without an increase of hypoglycemic episodes compared to computerized [13], [15] and paper-based [21], [49], [50] best practice studies.

Even though the insulin dosing algorithm compared similar or superior to best practice studies room for improvement was detected. Especially the detailed evaluation of safety and effectiveness of individual decision support steps of the insulin dosing algorithms revealed that there were still bolus injections resulting in BG levels outside the extended target range. The vast majority of BG values outside the extended target range was in the hyperglycemic range, and potentially resulted from too small insulin doses not covering the patients' meal BG rise. Especially in the first days some patients received too little insulin calculated by the insulin dosing algorithm. For these patients the safety measure of restricting the TDD increase by 20% limited the optimal dose finding during the patients' short hospital stay. Therefore, improvement in dose finding at the patients' therapy enrollment would significantly improve the patients' diabetes therapy.

The methodology for calculating the first TDD is very generic and therefore based only on the patients' weight, age and serum creatinine level. This rule based methodology is based on the initial treatment protocol of Umpierrez et al. [21]. By comparing the patients' insulin starting dose with the dose on the 6th study day and relating age and serum creatinine in a linear regression model, no significant relationship between these parameters and the patients' "true" insulin demand could be established. In this preliminary and unpublished investigation, "true" insulin demand was defined as the insulin dose on the 6th study day, because the TDD on the 6th study day had sufficient time to develop into a steady state and to achieve a 50:50 basal to bolus ratio. Validations of age and serum creatinine in the model

did not confirm the rules for therapy initialization by Umpierrez et al. using clinical data. However, to minimize the risk for hypoglycemia in elderly patients the insulin starting dose is reduced, which is also recommended by Pozzilli et al. [51]. Future versions of the insulin dosing algorithm should target to improve this insulin dose finding process at the start of the diabetes therapy and should incorporate more relevant and patient-specific parameters.

Unfortunately, also by using the refined version of the insulin dosing algorithm in some patients mild hypoglycemic events occurred indicating that these patients received too much insulin. Hypoglycemia occurred during all times of the day and was not only emerging from patients with already low BG levels, but also occurred in patients with initially high BG values. The initial problem of an increased probability to experience hypoglycemia in the afternoon was reduced by redistributing the daily bolus insulin. Reasons for hypoglycemia may be manifold and my investigations to derive predictors failed. However, one reason for too much insulin in some patients could be the generic supplemental insulin scheme. In patients with a small TDD the rigid scheme results in proportionally larger supplemental insulin doses than in patients with a high TDD. Furthermore, only few HCPs modified the insulin sensitivity parameters in GlucoTab® and left out possibilities for personalization of the patients' therapy. That may be reasons for insufficiently controlled hyperglycemia, but may also be reasons for too much insulin resulting in hypoglycemia. **Figure 16** indicates that on average the amount of supplemental insulin in the higher glycemic regions was not sufficient to control hyperglycemia. But by additionally considering the individual dosing decisions in these regions, a few patients received too much insulin which resulted in hypoglycemia, **Figure 15**. Assisted selection of the patients' parameter for insulin sensitivity may be a way to achieve safer and better control by using the current supplemental insulin scheme. For example, if on two days in a row the glycemic targets were not achieved with additional corrective insulin the treating physician gets a suggestion to adjust the parameter of the patients' insulin sensitivity. Individualization of the supplemental bolus insulin scheme, e.g. by using corrective bolus insulin in relation to the patients' TDD could also potentially increase safety and effectiveness of the therapy.

Personalization of diabetes therapy is key to further improve the patients' diabetes therapy. However, many factors are affecting the therapy of T2DM patients and especially in institutional care personalization only plays a secondary role due to the patients' short hospital stay and rigid workflows. Chapter IIV discusses relevant parameters for personalization of diabetes therapy and how decision support systems could support this process. Future work for improving the insulin dosing algorithm

should focus especially on deriving robust parameters for dose finding on the first therapy day, and to identify problematic patients in advance, e.g. to increase the BG measurement interval and to make HCPs aware of factors for therapy personalization.

CHAPTER IV

Testing the capability of continuous glucose monitoring to assess the clinical impact and safety of basal-bolus insulin therapy

This chapter is partly taken from a previously published article (Schaupp*, **Donsa*** et al. 2015 [47]) and is complemented by so far unpublished data. For the first time we investigated safety and clinical impact of an algorithm driven basal-bolus insulin therapy using CGM in a large sample of hospitalized T2DM patients to derive improvements for insulin dosing.

Glucose values in the published article (Schaupp*, **Donsa*** et al. 2015) are displayed in mmol/L. All other investigations in this PhD thesis are displayed in mg/dL. Conversions between the units are provided where necessary.

* Both authors contributed equally to this study.

1. Taking a Closer Look - Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients with Type 2 Diabetes Mellitus Under Basal-Bolus Insulin Therapy [Schaupp, Donsa et al. 2015]

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 17, Number 8, 2015

DOI: 10.1089/dia.2014.0343

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Taking a Closer Look—Continuous Glucose Monitoring in Non-Critically Ill Hospitalized Patients with Type 2 Diabetes Mellitus Under Basal-Bolus Insulin Therapy

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Abstract

Background: Inpatient glucose management is based on four daily capillary blood glucose (BG) measurements. The aim was to test the capability of continuous glucose monitoring (CGM) for assessing the clinical impact and safety of basal-bolus insulin therapy in non-critically ill hospitalized patients with type 2 diabetes mellitus (T2DM).
Materials and Methods: Eighty-four patients with T2DM (age, 68 ± 10 years; glycosylated hemoglobin, 72 ± 28 mmol/mol; body mass index, 31 ± 7 kg/m^2) were treated with basal-bolus insulin. CGM was performed with the iPro®2 system (Medtronic MiniMed, Northridge, CA) and calibrated retrospectively.
Results: A remarkable consistency between CGM and BG measurements and therapy improvement was shown over the study period of 501 patient-days. The number of CGM and BG measurements (CGM/BG) in the range from 3.9–10 mmol/L increased from 67.7%/67.2% (on Day 1) to 77.5%/78.6% (on the last day) ($P < 0.04$). The number of low glycemic episodes (3.3 to <3.9 mmol/L) during nighttime detected by CGM was 15-fold higher, and the number of episodes >13.9 mmol/L detected by CGM during night was 12.5-fold higher than the values from the BG measurements. Ninety-nine percent of data points were in the clinically accurate or acceptable Clarke Error Grid Zones A + B, and the relative numbers of correctly identified episodes of <3.9 and >13.9 mmol/L detected by CGM (sensitivity) were 47.3% and 81.5%, respectively.
Conclusions: Our data exhibit a good agreement between overall CGM and BG measurements, but there were a high number of missed hypo- and hyperglycemic episodes with BG measurements, particularly during nighttime. Overall assessment of glycemic control using CGM is feasible, whereas the use of CGM for individualized therapy decisions needs further improvement.

Background

Around 20% of hospital inpatient days occur in patients with diabetes. These patients have an increased risk to undergo adverse events such as hyper- or hypoglycemia during a hospital stay.[1–3] Observational and randomized controlled studies indicate that improvement in glycemic control results in lower rates of hospital complications in general medicine and surgery.[4,5]

Nevertheless, glucose management in the hospital setting is still far from ideal.[6] One of several obstacles for improvement of glycemic control in the hospital is the common belief that short-term poor glycemic control is an unavoidable consequence of acute illness rather than a condition in need of treatment.[7]

Current guidelines recommend the implementation of a standardized insulin order set in the inpatient glucose management and favor a scheduled subcutaneous basal and nutritional

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Parts of this study were presented at the 7th International Conference on Advanced Technologies and Treatments for Diabetes, held February 5–8, 2014, in Vienna, Austria.
This study is registered with ClinicalTrials.gov with clinical trial registration numbers NTC01407289, NCT01766752, and NCT01932775.

bolus insulin therapy with a premeal blood glucose (BG) value of less than 7.8 mmol/L and a random BG value of less than 10 mmol/L.[8] In this regimen, prandial insulin dosing decisions are facilitated by four capillary finger-stick BG measurements: one before each meal and one at bedtime. This four-point daily BG profile is capable of safely running a basal-bolus insulin regimen.[9–11] However, it only provides a sequence of snapshots of the patient's glycemia and does not represent the complete complex pattern of the various BG levels.[12,13]

In contrast, continuous glucose monitoring (CGM) is capable of displaying the complete diurnal glycemic profile and of detecting patterns of responsiveness to therapeutic efforts.[14] In addition, with real-time CGM, the incidence of hypo- and hyperglycemic events could be reduced. In a recent randomized controlled trial insulin treatment was even guided by CGM in critically ill patients.[15] Although designed to be a management tool for individuals with diabetes, CGM is also a potentially valuable tool for the assessment of the outcomes of clinical studies.[16] Therefore we used CGM to closely monitor glucose excursions generated by an integrated basal-bolus insulin dosing algorithm based on capillary BG measurements.

The aim of the present investigation was to test the capability of CGM for assessing the potential clinical impact and safety of an algorithm-driven basal-bolus insulin regimen including the detection of hypo- and hyperglycemic episodes in non-critically ill hospitalized patients with type 2 diabetes mellitus (T2DM).

Materials and Methods

Research design

The investigation was conducted at the general ward of the Division of Endocrinology and Metabolism at the Department of Internal Medicine (Medical University of Graz, Graz, Austria), was approved by the local ethics committee, and was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Patients gave written informed consent after the purpose, nature, and potential risks of the study had been explained and before any study-related activities were started.

Adult patients with an age of ≥18 years with T2DM who were treated with diet alone and/or with any oral or injectable antihyperglycemic therapy and who were admitted to the general ward were included in the trial. Main exclusion criteria were as follows: any mental condition rendering the patient incapable of giving consent, pregnancy, type 1 diabetes, or any disease or condition that the investigator or treating physician felt would interfere with the trial or the safety of the patient. The study ended with hospital discharge, with the transfer of the patient to a different ward, or after 21 days.

Algorithm-driven basal-bolus insulin treatment

Patients were treated with a workflow-integrated basal-bolus insulin algorithm that aims for fasting and premeal glucose levels of 5.6–7.8 mmol/L and that has been described in detail previously.[9,11] In brief, total daily dose was adjusted once daily by the algorithm based on the BG values of the preceding 24 h. The calculated total daily dose was divided in a 1:1 ratio into daily basal and daily bolus insulin dose. The bolus dose was distributed among the three meals (breakfast, lunch, dinner). In case premeal glucose values were below the target range, the insulin bolus was reduced, whereas glucose values above the target range induced an additional corrective bolus dose.

Glucose measurements (capillary BG, CGM)

Glucose control was based on four daily capillary BG finger-stick measurements (three premeal and one bedtime measurement) using a point-of-care testing device (ACCU-CHEK® Inform system; Roche Diagnostics, Basel, Switzerland) integrated into the hospital information system. In addition to these scheduled BG measurements, nurses were able to perform further glucose measurements at any time, if considered necessary.

Additionally, glucose was monitored with a blinded CGM system (iPro®2 system; Medtronic Minimed, Northridge, CA) that records a glucose value in the interstitial fluid every 5 min. CGM sensor insertion was performed according to the manufacturer's instructions on the first study day. If a patient's participation in the study exceeded the manufacturer-specified sensor lifetime of 6 days, a new sensor was inserted to allow CGM throughout the whole study period. CGM was only temporarily discontinued when patients had to undergo diagnostic procedures (e.g., computed tomography, magnetic resonance imaging). Anonymized data were processed using the Medtronic CareLink™ software. Sensor data were calibrated retrospectively based on the four daily BG measurements. Thereby, neither the staff nor the patients were able to see the CGM glucose values, trends, and profiles during the insulin treatment.

Definition of the target range and hypo- and hyperglycemic episodes

The target range for the insulin-dosing algorithm was defined to be from 5.6 to 7.8 mmol/L. For the analysis, a recommended extended target range from 3.9 to 10.0 mmol/L was used.[8,9,11] Hypo- and hyperglycemic episodes were defined as at least three consecutive CGM readings below or above a given threshold.[17] Thresholds for hypoglycemia were glucose values of <2.8/3.3/3.9 mmol/L, and hyperglycemia was defined by glucose values of >13.9 mmol/L.

Data analysis

The dataset consisted of the BG measurements and the CGM readings. To be eligible for analysis, at least 70% of the CGM measurements had to be available per day. Furthermore, at least two eligible days of CGM measurements had to be available per subject. The data selection process is displayed in Supplementary Figure S1 (Supplementary Data are available online at www.liebertonline.com/dia). Glucose profiles were analyzed based on the recommendations for standardizing the analysis and presentation of glucose monitoring data.[17] The analysis was performed with all CGM and BG values, and the values from the first and the last full 24-h treatment day were compared with each other. The average glucose value over the 24-h profile was calculated for the CGM data. The average of the premeal, the bedtime, and additional measurement values was calculated from the BG measurements. In addition, the quantile ranges (25–75% and

10–90%) were displayed graphically (Fig. 1). Glucose variability was calculated either as SD or as coefficient of variation ([SD/mean] × 100%) of the CGM and the BG data. Values in different ranges were defined as ''% of readings'' within a well-defined range.

Clinical point accuracy was evaluated using the Clarke Error Grid.[18] Sensitivity and specificity were calculated with paired CGM and capillary BG values as described by Zijlstra et al.[19] Pearson's χ^2 tests were used to analyze the nominal data. Fisher's exact test was computed when a table had a cell with an expected frequency of <5. Prior to data analysis, all metric outcome variables were checked for normality by means of a Shapiro–Wilk's test. Nonparametric tests were applied if the metric variables were not distributed normally. We used the Wilcoxon's signed-rank test for matched samples. The level of significance was set to 5% for all tests. Spearman correlations were used to compare BG measurements and CGM metrics. Statistical analysis was performed using R version 2.15.0 software.[20]

Results

Included in the analysis were 140,424 CGM and 2,066 BG measurement values. This corresponds to 501 patient-days of 84 patients under basal-bolus insulin treatment in hospital care. Except otherwise stated all analysis was done with the full dataset. The detailed baseline characteristics are given in Table 1.

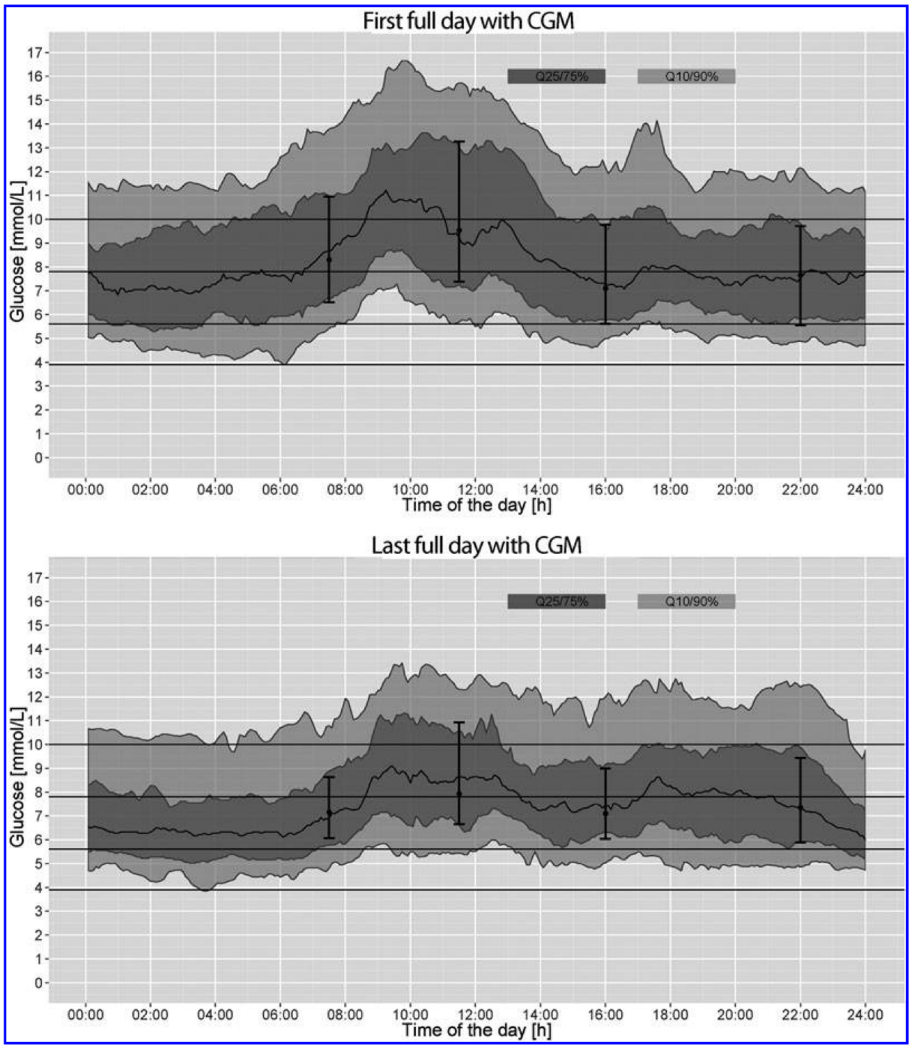

FIG. 1. Continuous glucose monitoring (CGM) profiles and blood glucose measurements for the first and the last day of algorithm-guided basal-bolus insulin treatment. The line at the glucose level of 3.9 and 10 mmol/L marks the threshold for hypo-/hyperglycemia, and the lines at 5.6 and 7.8 mmol/L represent the recommended target range. CGM values are median ± interquartile range (25–75% [Q25/75%] and 10–90% [Q10/90%]). Blood glucose values are median ± interquartile range (25–75%), displayed as bars.

Table 1. Clinical Characteristics

Characteristic	*Value*
n	84
Gender (F/M) (*n*)	32/52
Age (years)	68.5 ± 10.3
BMI (kg/m^2)	31.0 ± 6.6
Weight (kg)	89.1 ± 18.8
Race (white/other) (*n*)	82/2
Serum creatinine (mg/dL)	1.5 ± 1.0
HbA1c (mmol/mol)	72.8 ± 28.2
Diabetes duration (years)	15.1 ± 11.1
Admission diagnosis (%)	
Cardiovascular disease	31.3
Endocrine disorder	25.0
Infectious diseases	30.2
Gastrointestinal disease	1.0
Other	12.5
Length of stay (days) [median (25th; 75th percentile)]	7.5 (6; 12)
Total daily insulin (first/last day) (IU)	
Basal	24 ± 16/27 ± 24
Bolus	32 ± 21/29 ± 22
Patients with corticosteroids first/last day (*n*)	4/3

Data are mean ± SD values unless otherwise indicated.
BMI, body mass index; F, female; HbA1c, glycated hemoglobin; M, male.

Glucose profile and hypo- and hyperglycemic episodes

The 24-h glucose profile is shown for the first and the last treatment day (Fig. 1), including the 3.9 and 10 mmol/L threshold and the target range from 5.6 to 7.8 mmol/L. The parameters of the quantitative assessment of glycemic control by CGM and BG measurements are shown in Table 2.

Overall, 75.8% and 73.2% of CGM and BG readings were within the range from 3.9 to 10.0 mmol/L, with a significant improvement over time from 67.7%/67.2% (CGM/BG) on the first day to 77.5%/78.6% (CGM/BG) on the last day ($P < 0.04$). This improvement was not associated with a significant increase of hypoglycemic episodes <3.9 mmol/L from the first day (2.6%/1.7%, CGM/BG) to the last day (2.8/1.2%, CGM/BG) ($P > 0.2$). Furthermore, there was a significant decrease of BG values >10.0 mmol/L from the first (29.7/31.1%, CGM/BG) to the last (19.7/20.1%, CGM/BG) day ($P < 0.04$). Glucose variability expressed by the coefficient of variation significantly improved over time from 39.6/40.6% (CGM/BG) on the first day to 36.9/36.8% (CGM/BG) on the last day ($P < 0.03$ and $P = 0.05$, respectively [CGM/BG]) which is also reflected by the reduced interquartile ranges in Figure 1.

A distribution of episodes <2.8, from 2.8 to <3.3, from 3.3 to <3.9, and >13.9 mmol/L assessed by BG and CGM glucose values is given in Figure 2. The number of observed glycemic episodes during night between 3.3 and <3.9 mmol/L increased 15-fold, and the number of observed episodes >13.9 mmol/L increased 12.5-fold by using CGM compared with the BG measurements. During daytime this difference was not that pronounced. Most episodes <3.9 mmol/L occurred during nighttime, whereas most episodes >13.9 mmol/L were recorded during daytime. Duration of low glycemic events was longer during nighttime (Supplementary Table S1).

Accuracy of CGM versus capillary BG measurements

For assessment of the CGM accuracy, 2,007 pairs of BG and CGM values were available. The absolute differences between the data from the CGM and the BG measurements are shown in Figure 3. The median difference over all data was 0 mmol/L, but a systematic bias with too high CGM values in the hypoglycemic range and too low CGM values in the hyperglycemic range has been observed. In the low glycemic range the median offset was up to +0.5 mmol/L; in the high glycemic range the median offset was up to −0.8 mmol/L. Numerical point accuracy stratified by glucose level is given in Supplementary Table S2, expressed by mean absolute difference, mean absolute relative difference, median absolute difference, and median absolute relative difference.

Table 2. Comparison Between Continuous Glucose Monitoring and the Capillary Blood Glucose Measurements

	Overall		*First day*		*Last day*	
	CGM	*BG*	*CGM*	*BG*	*CGM*	*BG*
Patients (*n*)	84	84	84	84	84	84
Glucose values (*n*)	140,424	2,066	23,686	351	23,301	323
Average glucose (mmol/L)	8.1	8.3	8.7	8.9	7.9	8.1
Glucose variability SD (mmol/L)	3.1	3.2	3.5	3.6	2.9	3.0
Coefficient of variation (%)	37.7	38.6	39.6	40.6	36.9	36.8
<2.8 mmol/L (%)	0.3	0.2	0.5	0.0	0.4	0.0
<3.3 mmol/L (%)	0.8	0.7	1.2	0.3	0.9	0.6
<3.9 mmol/L (%)	2.4	2.7	2.6	1.7	2.8	1.2
3.9–10.0 mmol/L (%)	75.8	73.2	67.7	67.2	77.5	78.6
5.6–7.8 mmol/L (%)	36.2	33.5	30.7	31.9	37.9	37.5
>10.0 mmol/L (%)	21.9	24.1	29.7	31.1	19.7	20.1
>13.9 mmol/L (%)	5.6	5.9	8.6	10.0	3.7	3.4
>19.4 mmol/L (%)	0.5	0.6	0.9	1.1	0.4	0.6

Blood glucose (BG) and continuous glucose monitoring (CGM) measurements over the whole study period (overall) and for the first and the last day of treatment are shown.

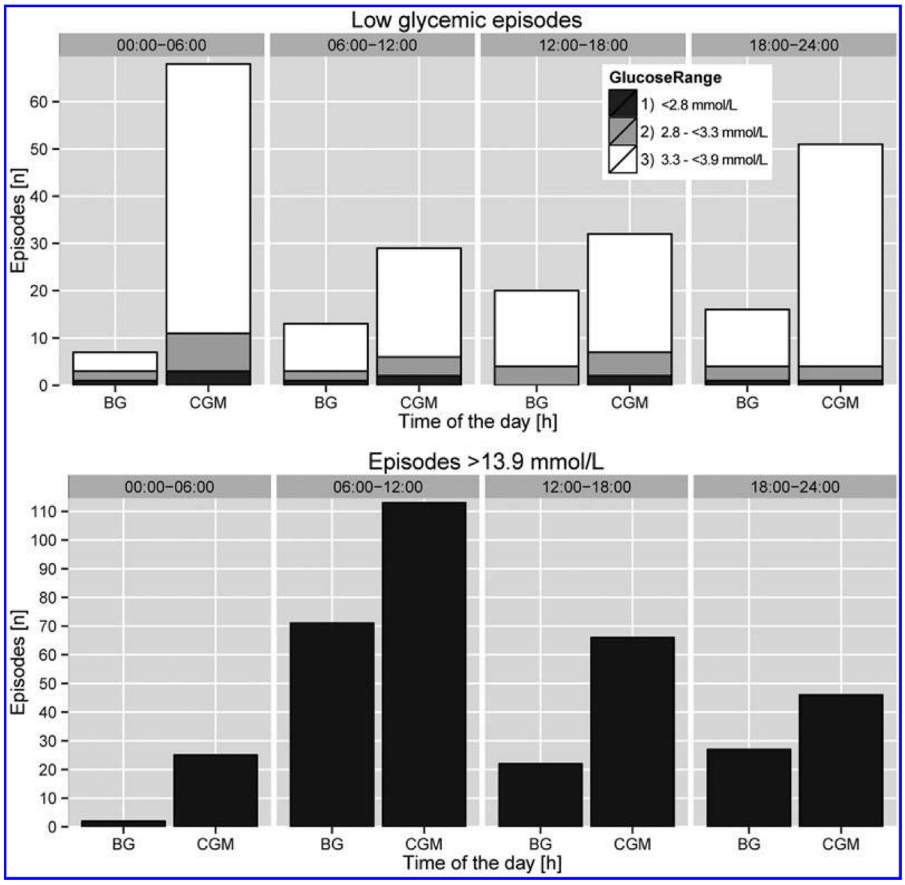

FIG. 2. Diurnal distribution of glycemic episodes <2.8, from 2.8 to <3.3, from 3.3 to <3.9, and >13.9 mmol/L detected by continuous glucose monitoring (CGM) and blood glucose (BG) measurements.

Clarke Error Grid analysis was performed to assess the clinical accuracy (Supplementary Fig. S2). The percentage of clinically accurate (Zone A) or acceptable (Zone B) values was 98.7%, with 88.2% of the values located within Zone A. The remaining values were in the not acceptable Zone D (1.4%). No values were found in Zone C or E. The correlation coefficient between CGM and corresponding BG values was 0.94.

Characteristics for the CGM system to detect episodes for different thresholds are given in Supplementary Table S3. The sensitivity to detect glucose below 3.9 mmol/L was 47.3% (CGM could accurately identify 26 out of the 55 total hypoglycemic events identified by BG measurements). However, 25 of the 51 CGM values <3.9 mmol/L were not confirmed with BG values, which would result in a false alarm rate of 49.0%. In contrast, the sensitivity to detect glucose values greater than 13.9 mmol/L was 81.5% (CGM could accurately identify 97 out of the 119 total events >13.9 mmol/L identified by BG measurements).

Discussion

Clinical impact and consistency

Basal-bolus insulin therapy improved patients' glycemia, which is demonstrated by a high number of CGM as well as BG readings (77.5%/78.6% CGM/BG) in the range of 3.9–10.0 mmol/L at the end of the hospital stay without compromising hypoglycemia. Furthermore, the therapy led to a decrease of hyperglycemia and a stabilization of the BG values, as expressed by a low coefficient of variation, which is associated with a better clinical outcome.[21–23] A possible explanation is the titration of insulin to the actual insulin need by adapting the basal and bolus insulin. The total daily injected insulin did not change between the first and the last day, but the ratio between basal and bolus insulin: basal insulin was slightly increased, whereas bolus insulin was decreased during the hospital stay (Table 1). A remarkable consistency between the parameters describing the overall therapy performance obtained by CGM and BG measurements was found, even though the number of CGM values was 70-fold higher than the number of BG measurements.

Safety

The amount of detected hypo- and hyperglycemic episodes differs significantly between the two methods. By using CGM, a substantial additional proportion of low glucose values during nighttime (00:00–06:00 h) was identified: the number of episodes between 3.3 to <3.9 mmol/L increased

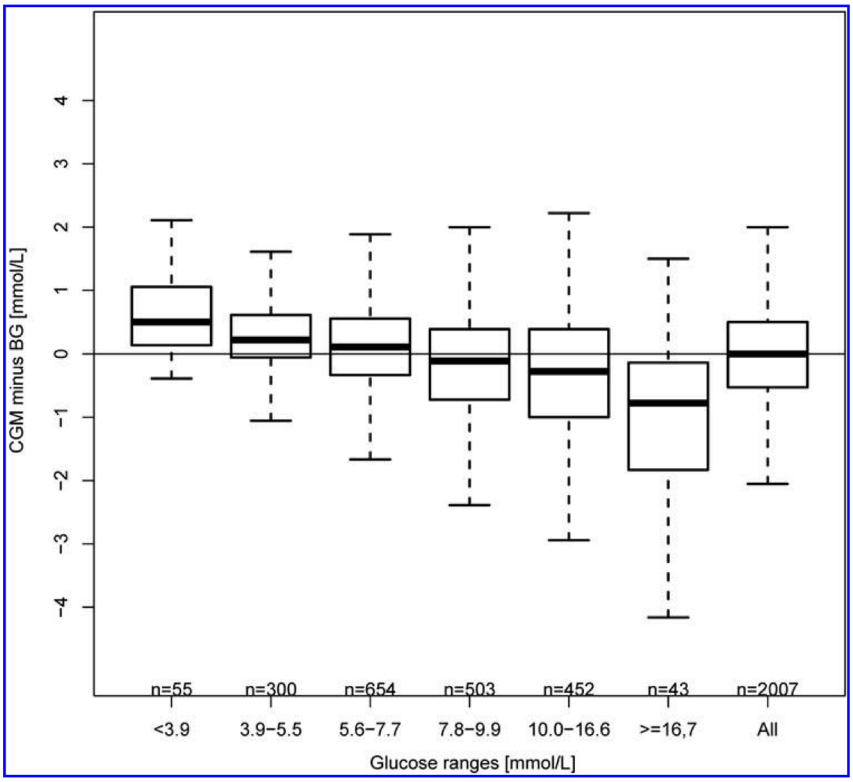

FIG. 3. Differences between continuous glucose monitoring (CGM) and blood glucose (BG) measurements over the different glycemic ranges. The bottom and top of the box represents the first and third quartile, the line in the box is the median, and the ends of the whiskers are the minimum and maximum of the data.

15-fold using CGM compared with BG measurements (62 vs. four episodes). With both measurements (CGM and BG), the number of hypoglycemic episodes <3.3/2.8 mmol/L was low, which implies that the algorithm can be considered as safe.

Because the CGM system was used for retrospective analysis, it was not possible to confirm all low CGM readings with BG measurements. Although this is a limitation of the study, a request to confirm low glycemia with BG measurements would have influenced the study due to possible interventions to correct for better glycemic control. Some reports in patients with type 1 diabetes suggest that CGM sensor inaccuracy overestimates the frequency of asymptomatic nighttime hypoglycemic episodes, and thus findings may be interpreted with caution.[24]

From a clinical perspective it is of great interest if the undetected low glycemic episodes during nighttime would have any influence on clinical decisions or even on the clinical outcome.[25–27] The present study did not aim to provide an answer to this, and it is therefore not possible to derive any conclusions referring to that from the available data.

As expected, the episodes <3.9 mmol/L lasted longer during nighttime, which may be explained by the fact that these episodes were not realized by the patient (asymptomatic) and that the periods without any BG measurements to correct for low glycemia are longer. Although the absolute number of observed episodes >13.9 mmol/L was low during nighttime (25 by CGM vs. two by BG), the number of episodes detected with CGM increased 12.5-fold compared with BG measurements. These findings suggest that high numbers of possibly clinically relevant episodes are missed because of the low number of measurements during nighttime, which is in good agreement with previous studies.[14,24,28]

Accuracy

Although the overall performance of the CGM system was acceptable as demonstrated with the error grid analysis and the numerical point accuracy (Supplementary Table S3), a closer look at the CGM data on the different glucose zones[29] revealed a positive bias for glucose values <5.6 mmol/L and a negative bias for values >10 mmol/L (Fig. 3). This leads to an underestimation of the number of hypo- as well as hyperglycemic episodes. Even with this finding high numbers of additional glycemic episodes <3.9 mmol/L and >13.9 mmol/L were detected with CGM as described previously. This implies that the number of undetected hypo- and hyperglycemic episodes could even be larger.

Reliable real-time CGM would enable timely detection and prevention of hyper- and hypoglycemia by triggering alarms. The theoretical false alarm rate and the ability to detect episodes with the CGM system used in the study were poor but comparable to the findings of Zijlstra et al.[19] Only every second episode <3.9 mmol/L was correctly detected.

Consequently, every second alarm would have been false, which is not acceptable from a clinical point of view.

It may be argued that the accuracy of the CGM system is influenced by the different days of wear (accuracy is lowest on Day 1 after insertion of the sensor); thus the length of stay may influence the accuracy analysis. Because the CGM systems were calibrated retrospectively, the possible drifts of the sensors were leveled out, which was confirmed by the fact that the difference between CGM and BG measurements was not increased during the first days after sensor insertion (data not shown). Furthermore, after 6 days a new sensor was inserted, which means that a longer length of stay is not necessarily associated with a longer wear time of a single sensor.

The limitations of the poor measuring accuracy of the CGM system are partly compensated for by the fact that data were derived in a highly standardized environment at a general ward with strict adherence to everyday procedures. This is a prerequisite to average the individual data of the subjects, which combines intra- as well as intersubject variability.[30] Therefore, the data describe very well the overall daily routine, such as the BG level rise after meals and the impact of the applied therapy on glucose management. This is also reflected by the good agreement between the CGM and BG measurements as shown in Figure 1 and by the Clarke Error Grid analysis.

One of the key issues of good glycemic control is to have enough data available for the decision making to be able to assess the quality of the glycemic control with an acceptable effort.[31] Standard care is currently based on four capillary BG measurements (three premeal measurements and one measurement before bedtime). Possibly clinically relevant episodes, such as hypo- or hyperglycemia between the spot measurements, are missed. Manpower issues and inconvenience for the patient restrict frequent BG monitoring, and thus CGM could be an attractive alternative to the BG measurements or can be used as a supplementary method.[13] Although promising, CGM alone is not recommended for glucose management by the guidelines for hospitalized patients at this time until further studies provide sufficient evidence for its accuracy and safety.[4,32]

In conclusion, it was demonstrated that the CGM and BG data showed overall high consistency over the whole study period, which enables assessment of the clinical impact of insulin therapy with CGM in more detail. Undetected hyper- and hypoglycemic episodes during periods of low frequency of BG measurements suggest the use of CGM in the hospital. However, the poor performance of the existing systems on an individual basis and the lack of evidence for the clinical relevance of the missed episodes lead to the conclusion that more accurate systems and further clinical studies are needed before CGM can be recommended for use in this patient population.

Acknowledgments

The authors thank the physicians and nurses at the Division of Endocrinology and Metabolism for their help in the performance of the study, B. Tschapeller for data management, B. Boulgaropoulos for critical review and editorial assistance with the manuscript (both with Joanneum Research GmbH), and A. Berghofer (Medical University of Graz) for data monitoring. This study was funded by the European Commission project REACTION (FP7 248590).

Author Disclosure Statement

T.R.P. is a member in the advisory board of NovoNordisk A/S and received speaker honoraria from NovoNordisk A/S. J.P. received speaker honoraria from NovoNordisk A/S. J.K.M. received speaker honoraria from NovoNordisk A/S and Roche Diagnostics. L.S., K.D., K.M.N., F.A., B.H., S.S., T.A., and P.B. declare no competing financial interests exist.

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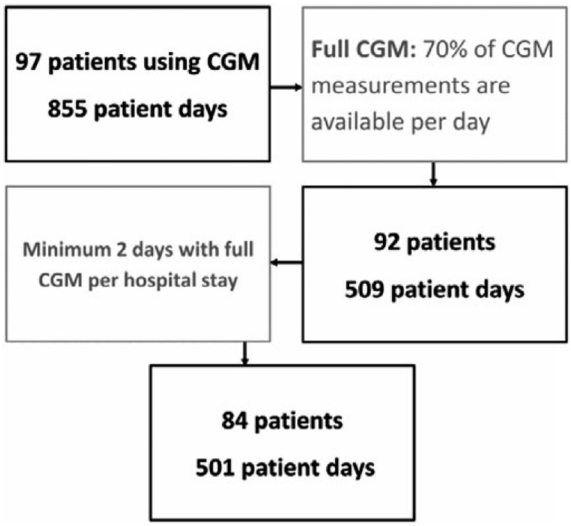
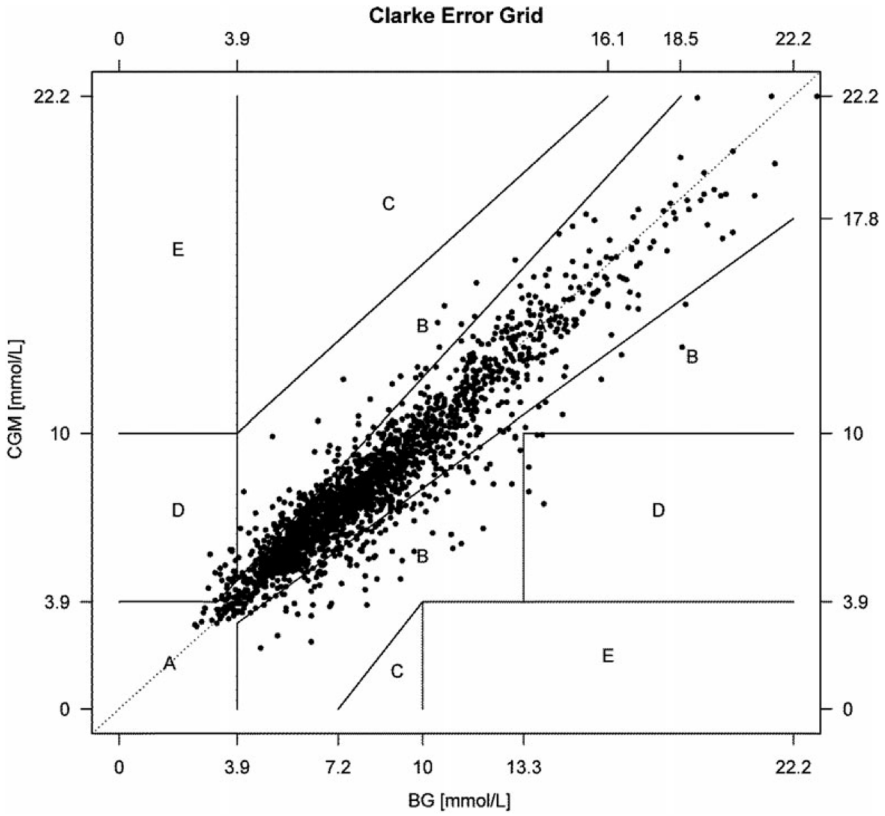
Supplementary Data



SUPPLEMENTARY FIG. S1. Data selection. CGM, continuous glucose monitoring.



SUPPLEMENTARY FIG. S2. Clarke Error Grid analysis. BG, blood glucose; CGM, continuous glucose monitoring.

Supplementary Table S1. Number of Glycemic Episodes (<2.8, 2.8 to <3.3, 3.3 to <3.9, and >13.9 mmol/L) and Duration (<1, 1–2, and >2 h) Detected by Continuous Glucose Monitoring

	00:00–06:00			*06:00–12:00*			*12:00–18:00*			*18:00–24:00*		
Level (mmol/L)	*< 1 h*	*1–2h*	*> 2 h*	*< 1 h*	*1–2 h*	*> 2 h*	*< 1 h*	*1–2 h*	*> 2 h*	*< 1 h*	*1–2 h*	*> 2 h*
<2.8	1	1	1	0	2	0	0	1	1	0	1	0
2.8 to <3.3	1	0	7	2	1	1	0	4	1	2	0	1
3.3 to <3.9	31	15	11	19	3	1	18	5	2	30	11	6
>13.9	8	4	13	44	23	46	15	20	19	9	18	8

Supplementary Table S2. Numerical Point Accuracy Expressed by Mean Absolute Difference, Mean Absolute Relative Difference, Median Absolute Difference, and Median Absolute Relative Difference

Reference glucose (mmol/L)	*MAD (mmol/L)*	*MARD (%)*	*MedAD (mmol/L)*	*MedARD (%)*
All	0.76	9.6	0.50	6.5
<3.9	0.73	21.3	0.50	16.3
3.9–10.0	0.66	9.6	0.44	6.8
>10.0	1.08	8.4	0.72	5.8

MAD, mean absolute difference; MARD, mean absolute relative difference; MedAD, median absolute difference; MedARD, median absolute relative difference.

Supplementary Table S3. Continuous Glucose Monitoring Sensor Characteristics to Detect Episodes for Different Threshold

Threshold (mmol/L)	*TP*	*TN*	*FP*	*FN*	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*
<3.9	26	1,927	25	29	47.3	98.7	97.3
<3.3	5	1,988	5	9	35.7	99.7	99.3
<2.8	0	2,001	3	3	0	99.9	99.7
>13.9	97	1,863	25	22	81.5	98.7	97.7

There were 2,007 paired continuous glucose monitoring and blood glucose readings to be analyzed. The first column represents the thresholds to be detected by the sensor. Sensitivity was defined as $(TP/[TP+FN])\times 100\%$, specificity was defined as $(TN/[FP+TN])\times 100\%$, and accuracy was defined as $([TP+TN]/n)\times 100\%$, where TP is number of true positives, TN is number of true negatives, FP is number of false positives, FN is number of false negatives, and n is number of paired glucose readings (continuous glucose monitoring and blood glucose measurements).

2. Use of CGM for insulin dosing decisions – What-if analysis

This chapter provides analyses investigating the effect on insulin dose calculations based on glycemic information from CGM instead of BG measurements obtained by hospital glucose monitoring devices. The previous section already provided detailed analysis on the performance of the used CGM system (iPro®2 system; Medtronic Minimed, Northridge, CA). Clarke error grid analysis was performed to assess the clinical accuracy. Numerical point accuracy for different glycemic ranges was assessed, expressed by mean absolute difference, mean absolute relative difference and median absolute relative difference. Additionally, characteristics for the CGM system to detect episodes for different thresholds were derived. However, theses analyses do not relate the effect of deviating glucose information on the calculation of insulin doses.

The following analyses aim to investigate if the used CGM system could be used for running a basal-bolus insulin regimen. Different methods were developed to display the effect of insulin dose calculations based on CGM when comparing them to reference calculations. Recalculations of insulin doses were performed with the framework for workflow simulation described in Chapter II.

For analysis, all patients (n=59) treated with the initial version of the insulin dosing algorithm and where additional CGM was performed were included. In 13 patients the redistribution of the daily bolus insulin (Chapter III, section 2.1) was already tested. However, this did not influence the following investigations.

Recalculation of supplemental bolus insulin:

Recalculations of the supplemental bolus insulin dose using CGM data at the time of capillary BG measurement were possible for 84% of dose calculations. For the remaining supplemental insulin calculations was no CGM information available. The used supplemental insulin scheme is described in **Table AIII-2** in Appendix III.

Thirty-one percent of supplemental bolus insulin calculations were deviating from the reference calculations based on capillary BG, **Table 10**. The "degree of deviation" indicates if the insulin dose calculation based on CGM would have been in a higher or lower intervention border according to the used supplemental insulin scheme. A positive "degree of deviation" indicates an insulin dose increase

and a negative "degree of deviation" indicates a reduction. The supplemental insulin scheme is also demonstrated on the axes of **Figure 17**.

Table 10: Frequency of supplemental insulin calculations deviating from reference calculations based on capillary BG. The "degree of deviation" indicates if the insulin dose calculation based on CGM would have been in a higher or lower intervention border according to the used supplemental insulin scheme. Supplemental insulin dose according to glucose intervention border and insulin sensitivity [sensitive/normal/resistant]. All bolus insulin calculations; IU … Insulin Unit

Degree of deviation	Change of supplemental insulin dose	n	%
+3	+6/8/10 IU	2	0.1
+2	+4/6/8 IU	27	1.8
+1	+2/4/6 IU	204	13.8
±0	±0/0/0 IU	1,015	68.6
-1	- 2/4/6 IU	220	14.9
-2	- 4/6/8 IU	12	0.8
Total		1,480	

To assess the potential clinical impact of the deviating supplemental insulin calculations, an error grid was developed in cooperation with diabetes experts, **Figure 17**. The area "unacceptable treatment" indicates deviations resulting in ineffective treatment but unlikely potential patient harm. The area "major violations" indicates deviations resulting in very ineffective treatment or into moderate potential patient harm. The area "life threatening" indicates deviations leading to potential patient harm. The frequency of deviating mealtime bolus insulin calculations according to their potential clinical impact is demonstrated in **Table 11**.

Table 11: Potential clinical impact of calculations of mealtime bolus insulin based on CGM and compared to calculations based on capillary BG (reference). Areas according to the error grid indicate the severity of deviation from the reference calculation.

Area according to error grid:	Deviations	
	n	%
Acceptable treatment	830	81.9
Unacceptable treatment	59	5.8
Major violation	110	10.8
Life threatening	15	1.5
Total	1,014	

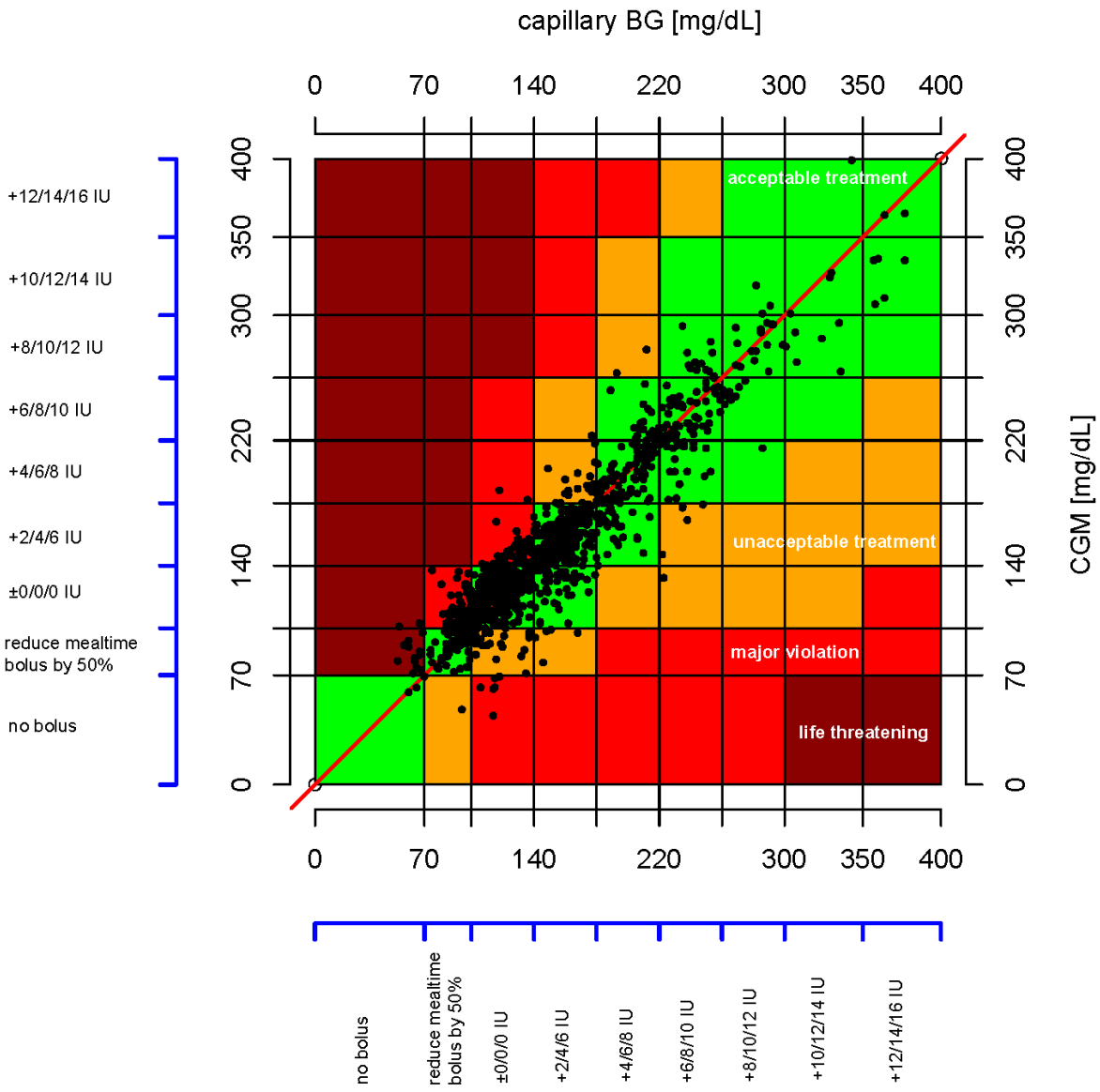


Figure 17: Error grid for evaluation of the potential clinical impact of bolus insulin calculations based on CGM. Areas indicate the severity of deviation. Only mealtime bolus insulin calculations displayed. Supplemental insulin dose according to glucose intervention border and insulin sensitivity [sensitive/normal/resistant]

Recalculation of the adjustment of the TDD:

Recalculations of the TDD using CGM data were possible for 78% of TDD calculations. For the remaining TDD adjustments no CGM information was available. The methodology for recalculation and analysis is illustrated in **Figure 18** and the procedure for adjustment of the TDD is described in Chapter III (section 2.2). The patients' TDD was recalculated in a what-if analysis using glycemic information from CGM and was compared to the originally calculated TDD based on capillary BG measurements.

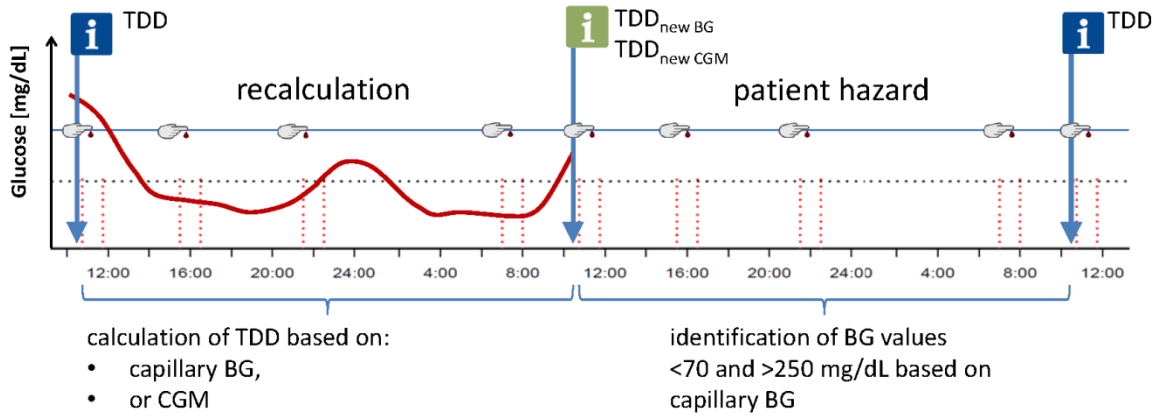


Figure 18: Methodology for recalculation and analysis of the adjustment of the TDD based on two different sources of glycemic information (CGM: continuous red line; BG: finger prick test symbol). Standard measurement times are demonstrated on the x-axis. BG values <70 and >250 mg/dL on the following day were used to detect potential patient hazard

A detailed comparison of the frequency of the TDD increase or decrease based on the used source of glycemic information is displayed in **Table 12**. Thirty-one percent of TDD calculations were deviating from the reference calculations. Thirty-two percent of TDD calculations would have been increased and 68% would have been decreased compared to the original calculations. The mean positive deviation was 6.5±3.3 IU (mean±SD) and the median positive deviation and range were 6 (1 – 14) IU. The mean negative deviation was 9.3±6.9 IU (mean±SD) and the median negative deviation and range were 7 (1 – 28) IU.

Table 12: Adjustment of the TDD based on glycemic information from CGM or capillary BG (reference). Numbers indicate the frequency. Sign and number imply percentage of TDD increase or decrease

TDD adjustment		Based on capillary BG				
		-20%	-10%	±0	+10%	+20%
Based on CGM	+20%	1	0	0	1	18
	+10%	1	0	10	62	3
	±0	13	5	130	12	0
	-10%	2	3	0	0	0
	-20%	15	5	38	8	2

Potential patient hazard was investigated by relating glycemic information (hypoglycemia and hyperglycemia) of the following day to the recalculation of the TDD, **Figure 19**. For this analysis the patients' last study day was excluded because on the last day no patient hazard analysis was possible. The recalculation of the adjustment of the TDD based on glycemic information from CGM for days

with hypo- or hyperglycemia is displayed in **Table 13**. Up to 14 additional IU (25.9% of the reference TDD calculation) would have been additionally ordered on days with hypoglycemia. Up to 28 IU (20.6% of the reference TDD calculation) would have been withheld on days with hyperglycemia. In 22.9% of days with hypoglycemia the use of glycemic information from CGM would have increased the insulin dose. In 26.9% of days with hyperglycemia the use of glycemic information from CGM would have decreased the insulin dose.

Table 13: Recalculation of the adjustment of the TDD based on glycemic information from CGM for days with hypoglycemia (<70 mg/dL) or hyperglycemia (>250 mg/dL)

	Hypoglycemia on the following day	Hyperglycemia on the following day
Days with TDD calculation based on CGM and hypo- or hyperglycemia: (n)	35	52
Reduced TDD compared to reference calculation: n / (%)	6 / (17.1%)	14 / (26.9%)
Increased TDD compared to reference calculation: n / (%)	8 / (22.9%)	3 / (5.8%)
Maximum additionally ordered: IU / (% of reference TDD)	14 / (25.9%)	9 / (27.3%)
Maximum withheld: IU / (% of reference TDD)	28 / (20.6%)	25 / (20.2%)

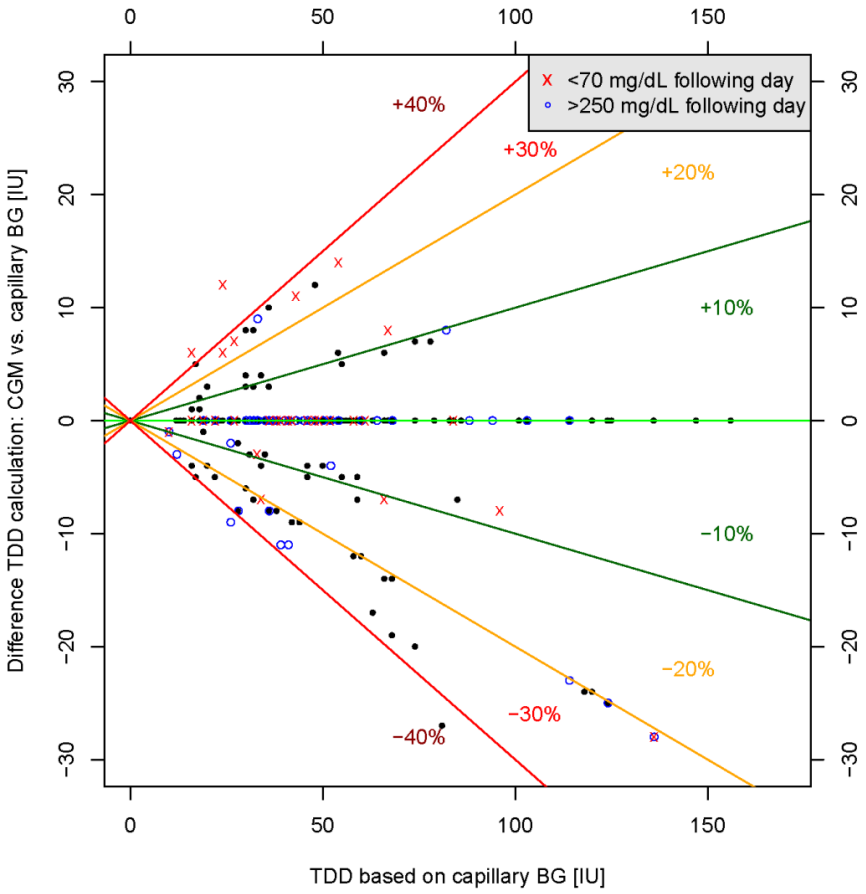


Figure 19: Difference of calculating the TDD based on CGM and capillary BG measurements over the reference TDD calculation. Patient hazard analysis by relating glycemic information of the following day.

3. Summary

A remarkable consistency was found between parameters that evaluate the performance of the basal-bolus therapy based on glycemic information from CGM and capillary BG measurements, even though the number of CGM values was 70-fold higher than the number of BG measurements. Pre-meal and bedtime BG measurements described the overall patients' glycaemia under basal-bolus insulin therapy sufficiently.

However, the amount of detected hypo- and hyperglycemic episodes differed significantly between the two methods. Especially during nighttime, a substantial additional number of glycemic events below 70 mg/dL were detected using CGM. These episodes lasted longer during nighttime, which may be explained by the fact that these episodes were not realized by the patient (asymptomatic hypoglycemia), and that there is a longer period without any BG measurement to correct for low glycaemia. This suggests that a high number of possibly clinically relevant episodes are missed. Staff shortages and inconvenience for the patients restrict more frequent capillary BG monitoring, and CGM could therefore be an attractive alternative to BG measurements or could be used as a supplementary method.

Although promising, CGM alone is not recommended for diabetes management by clinical guidelines [11], [52]. Also according to the investigations performed in the work of this PhD thesis, including analyses of the accuracy of the used sensor system and the effect of sensor inaccuracy on insulin dose calculations, the use of CGM for insulin dosing decisions in hospitals is currently not recommended. Although the overall performance of the CGM system was acceptable as demonstrated with the Clarke error grid analysis and numerical point accuracy, sensitivity to identify episodes <70 and >250 mg/dL were only 47.3% and 81.5%. Only every second episode <70 mg/dL would have been detected and if the system would have been used for alarming, every second alarm would have been false. This system performance is inacceptable from a clinical point of view.

Also in the what-if analysis recalculating insulin dosing decisions based on glycemic information from CGM, several potentially dangerous deviating insulin calculations were identified by comparing them to the reference calculations based on capillary BG measurements. Although this investigation is only hypothetical because the used CGM system was calibrated retrospectively and therefore no real-time use would have been possible, the sensor performance was comparable to sensor systems available at

the time of the clinical study [53]. For the evaluation of the potential impact of differences in calculation of insulin doses based on glycemic information from CGM, two methods were developed in collaboration with clinical diabetes experts. The first method is an error grid which categorizes deviations of bolus insulin calculations and relates their potential clinical impact. The use of CGM would have resulted in potentially life threatening insulin dose calculations (1.5%) and ineffective treatment (16.6%). The second method illustrates the deviation of calculating the patients' TDD based on CGM and BG measurements and relates glycemic information of the following day (hypo- and hyperglycemia).

Thirty-one percent of adjustments of the TDD were deviating from the reference calculations based on capillary BG measurements. By using CGM the TDD would have been decreased more often compared to the reference calculations, **Table 12**. This could have resulted in less insulin and potentially cause less hypoglycemia. But the investigation of the effect of the adjustment of the TDD based on CGM for days with hypoglycemia revealed, that only on few days with hypoglycemia the TDD would have been decreased. More often, in 22.9% of days with hypoglycemia, the use of glycemic information from CGM would have increased the insulin dose leading to potential patient harm. In 26.9% of days with hyperglycemia the use of glycemic information from CGM would have decreased the insulin dose leading to potentially ineffective treatment.

Hence, the results of these investigations highlight both opportunities and challenges for wider implementation of CGM, particularly if diabetes treatment and early hypoglycemia detection are the main drivers. Even though single point accuracy is limited, the information of glucose trends may still provide value [54]. In a randomized controlled trial at an intensive care unit (ICU) with 124 patients, hypoglycemia was reduced from 11.5% to 1.6% ($p=0.03$) when using real-time CGM compared to blinded CGM, with no difference in mean glucose levels [55]. This reduction in hypoglycemia was attributed to the use of the rate of change in glucose level to adjust the insulin infusion. In the recalculations of the patients' insulin doses no information of glucose trends was considered. The combination of BG measurements with high accuracy and CGM systems with high measurement frequency and trend information could also be beneficial for non-critically ill hospitalized patients with unstable glycaemia on a basal-bolus insulin regimen. The development of smart insulin dosing algorithms that consider glycemic trend information from CGM could improve insulin dosing and reduce hypo- and hyperglycemia.

By considering that CGM systems need frequent calibration based on capillary BG measurements and frequent sensor replacement, and additionally their high additional costs and their current lack of accuracy, the benefit of using CGM is limited in the majority of hospitalized T2DM patients [56]. New technological advances in this field, such as the introduction of a flash glucose monitoring device (FreeStyle® Libre™, Abbott Diabetes Care, Alameda, CA), providing high accuracy without the need of calibration by the user and a two week period of constant use, raise hopes that in near future these sensors will be approved for calculation of insulin doses [57].

CHAPTER V

Evaluation of the workflow and decision support system regarding safety, efficacy and usability – A clinical study

This chapter reprints the study findings as originally peer-reviewed published by Neubauer, Mader, Höll, Aberer, **Donsa** et al. 2015 [30]. Safety, efficacy and usability of GlucoTab® – a computerized workflow and decision support system – were investigated in a clinical study on different wards.

1. Standardized Glycemic Management with a Computerized Workflow and Decision Support System for Hospitalized Patients with Type 2 Diabetes on Different Wards [Neubauer, Mader, Höll, Aberer, Donsa et al. 2015]

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 17, Number 10, 2015
DOI: 10.1089/dia.2015.0027

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Standardized Glycemic Management with a Computerized Workflow and Decision Support System for Hospitalized Patients with Type 2 Diabetes on Different Wards

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Abstract

Background: This study investigated the efficacy, safety, and usability of standardized glycemic management by a computerized decision support system for non-critically ill hospitalized patients with type 2 diabetes on four different wards.

Materials and Methods: In this open, noncontrolled intervention study, glycemic management of 99 patients with type 2 diabetes (62% acute admissions; 41 females; age, 67 ± 11 years; hemoglobin A1c, 65 ± 21 mmol/mol; body mass index, 30.4 ± 6.5 kg/m^2) on clinical wards (Cardiology, Endocrinology, Nephrology, Plastic Surgery) of a tertiary-care hospital was guided by GlucoTab® (Joanneum Research GmbH [Graz, Austria] and Medical University of Graz [Graz, Austria]), a mobile decision support system providing automated workflow support and suggestions for insulin dosing to nurses and physicians.

Results: Adherence to insulin dosing suggestions was high (96.5% bolus, 96.7% basal). The primary outcome measure, percentage of blood glucose (BG) measurements in the range of 70–140 mg/dL, occurred in 50.2 ± 22.2% of all measurements. The overall mean BG level was 154 ± 35 mg/dL. BG measurements in the ranges of 60–70 mg/dL, 40–60 mg/dL, and <40 mg/dL occurred in 1.4%, 0.5%, and 0.0% of all measurements, respectively. A regression analysis showed that acute admission to the Cardiology Ward (+30 mg/dL) and preexisting home insulin therapy (+26 mg/dL) had the strongest impact on mean BG. Acute admission to other wards had minor effects (+4 mg/dL). Ninety-one percent of the healthcare professionals felt confident with GlucoTab, and 89% believed in its practicality and 80% in its ability to prevent medication errors.

Conclusions: An efficacious, safe, and user-accepted implementation of GlucoTab was demonstrated. However, for optimized personalized patient care, further algorithm modifications are required.

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This study is registered at Clinicaltrials.gov with clinical trial registration number NTC01932775.

Parts of this study were presented at the 74th Scientific Sessions of the American Diabetes Association, held in San Francisco, California, June 3–17, 2014, and the 14th Annual Diabetes Technology Meeting, held in Bethesda, Maryland, November 6–8, 2014. Parts of the continuous glucose monitoring (CGM) data were previously published.[1]

Background

Up to 35% of all hospitalized patients suffer from diabetes,[2,3] and hospital management costs for these patients place a serious financial burden to public healthcare systems.[4] In addition, patients with diabetes have an increased risk of infections,[5] prolonged hospital stays, and increased mortality due to insufficient insulin dosing management, which is caused by a varying degree of knowledge on glycemic control, clinical inertia, and the fear of hypoglycemia.[6] Considerable efforts have been made to improve glycemic management regarding blood glucose (BG) measurements, but an adequate insulin therapy in clinical practice is still lacking in many hospitals.[6,7]

Guidelines have been developed to improve glycemic management in hospitals that recommend a target range of less than 140 mg/dL for premeal BG and less than 180 mg/dL for a random BG measurement for non-critically ill patients treated with insulin.[8,9] These target ranges should be achievable by scheduled subcutaneous insulin dosing with basal, nutritional, and a correctional component.[8,9] The guidelines also suggest the development and evaluation of evidence-based computerized decision support systems, including computerized insulin and BG data display that will not only improve glycemic control but also workflow and communication among healthcare professionals.[6]

Paper-based algorithms for basal bolus insulin therapy have been developed that increase the quality of glycemic control and reduce hospital complications.[10–12] Within the framework of a European Commission–funded project (FP7 248590), we have modified and tested standardized recommendations of a paper-based insulin dosing algorithm to comply with daily workflow requirements on general wards.[13] This modified algorithm was then implemented in a mobile decision support system for basal bolus insulin dosing, the GlucoTab® system (Joanneum Research GmbH [Graz, Austria] and Medical University of Graz [Graz, Austria]), which was subsequently customized and tested in a clinical study with 30 patients.[14]

In the current study, the final mobile version of the GlucoTab system was used for the first time to guide the glycemic management process on four different general wards in the Departments of Internal Medicine and Surgery. The purpose of this study was to investigate the efficacy, safety, and usability of a standardized glycemic management with the GlucoTab system for non-critically ill patients with type 2 diabetes mellitus.

Materials and Methods

This study was an open, noncontrolled interventional study in hospitalized patients with type 2 diabetes mellitus. The study was conducted on four general wards of a tertiary-care hospital (Medical University of Graz). The participating wards were Endocrinology, Cardiology, Nephrology and Plastic Surgery, which are each independently managed by the respective division. All patients gave written informed consent prior to any study activity, and the study was approved by the ethical board of Medical University of Graz (protocol number EK-No. 25-344 ex 12/13). This study was conducted in full accordance with the principles of the Declaration of Helsinki.

Patient characteristics

The GlucoTab system was subsequently implemented on the four participating general wards. In total, 99 hospitalized patients were competitively recruited from May 2013 to December 2013. Hospitalized patients who met the inclusion criteria were included in the study after they consented to participate. The demographic and clinical characteristics of the study participants are presented in Table 1. Inclusion criteria were as follows: age ≥18 years and type 2 diabetes (treated with diet, oral antidiabetes drugs, non–insulin-injected antidiabetes drugs, insulin therapy, or any combination of the four therapies) or newly diagnosed hyperglycemia requiring subcutaneous insulin therapy. Patients were switched to insulin therapy in the case of hyperglycemia judged by the treating physician according to evidence-based recommendations to use insulin therapy as the preferred method for glycemic control in hospitalized patients.[8,9] Glycemic management with the GlucoTab system was not performed for patients with the following exclusion criteria: type 1 diabetes, gestational diabetes, any condition which the investigator or treating physician felt would interfere with the study or the safety of the patient, pregnancy, any mental condition rendering the patient incapable of giving consent, known or suspected allergy to insulin glargine or insulin aspart, continuous parenteral nutrition, or participation in another study that could interfere with this study.

Standardized glycemic management with GlucoTab

GlucoTab is a mobile computerized clinical decision support system for subcutaneous insulin therapy that supports nurses and physicians in glycemic management of hospitalized patients in two main tasks: First, it assists clinical healthcare professionals in organizing the treatment workflow of patients with type 2 diabetes mellitus by providing automated workflow support, including display for open tasks, facilitating documentation and providing visualization of BG values, nutrition and insulin doses. Second, it provides two standardized recommendations based on a basal-bolus insulin titration protocol[10–12,14] for (1) the total daily insulin dose, which is prescribed by the treating physician during the ward round, and (2) insulin dose suggestions for individual insulin administrations before each meal, at bedtime, and after intermediate BG measurements, if required. After confirmation of the suggested insulin dosage, the insulin is injected subcutaneously by an authorized nurse.

The standardized recommendations for insulin dose calculation, based on the modified basal bolus insulin titration protocol,[10–12,14] consist of a daily dose of basal insulin (insulin glargine; Sanofi-Aventis, Frankfurt am Main, Germany), bolus insulin (insulin aspart; NovoNordisk, Bagsværd, Denmark) before each meal, and a correctional dose at bedtime to achieve fasting and premeal BG values of less than 140 mg/dL.[8,9] Insulin therapy was started with a total daily dose of 0.5 units/kg of body weight. The initial total daily dose was reduced to 0.3 units/kg of body weight in patients ≥70 years of age and/or with creatinine values of ≥2.0 mg/dL. In case the patient had already been on insulin therapy, the protocol allowed use of the former total insulin dose as the initial dose, which could be adjusted by the treating physician. One-half of the total daily dose was administered as basal insulin once a day before lunch. The other half was administered as bolus

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Variable	*Total* (n = *99*)	*Nephrology* (n = *15*)	*Cardiology* (n = *30*)	*Endocrinology* (n = *42*)	*Plastic surgery* (n = *12*)	P
Gender, female [*n* (%)]	41/41	3/20	12/40	20/48	6/50	0.28
Ethnicity (Caucasian/African)	98/1	15/0	30/0	42/0	11/1	0.13
Age (years)	67 ± 11	64 ± 8	70 ± 12	67 ± 11	65 ± 10	0.31
Body mass index (kg/m^2)	30.4 ± 6.5	31.0 ± 5.4	29.4 ± 6.8	31.1 ± 6.8	29.4 ± 6.3	0.57
Weight (kg)	88 ± 21	92 ± 17	84 ± 24	89 ± 20	86 ± 17	0.22
Serum creatinine (mg/dL)	1.8 ± 1.5	3.8 ± 2.1	1.4 ± 0.9	1.6 ± 1.3	1.0 ± 0.2	< 0.05[a]
Renal dialysis (*n*)	9	6	1	2	0	—
HbA1c						0.13
mmol/mol	65 ± 21	57 ± 10	65 ± 21	70 ± 24	55 ± 13	
%	8.1 ± 4.1	7.4 ± 3.1	8.1 ± 4.1	8.6 ± 4.4	7.2 ± 3.3	
Diabetes duration (years)	13.6 ± 8.9	13.2 ± 8.3	11.4 ± 7.7	15.1 ± 9.6	13.9 ± 9.6	0.51
Pre-admission diabetes therapy [*n* (%)]						0.60
Diet only	3 (3)	0 (0)	1 (3)	2 (5)	0 (0)	
OAD only	16 (16)	0 (0)	6 (20)	8 (19)	2 (17)	
Insulin only	55 (56)	12 (80)	13 (44)	24 (58)	6 (50)	
OAD, GLP-1 analogs	1 (1)	0 (0)	0 (0)	1 (2)	0 (0)	
Insulin, OAD	22 (22)	3 (20)	9 (30)	6 (14)	4 (33)	
Insulin, GLP-1 analogs	2 (2)	0 (0)	1 (3)	1 (2)	0 (0)	
Admission type [*n* (%)]						< 0.05[b]
Planned	38 (38)	6 (40)	17 (57)	8 (19)	7 (58)	
Acute	61 (62)	9 (60)	13 (43)	34 (81)	5 (42)	
Admission diagnosis [*n* (%)]						—
Hematological disease	1 (1)	1 (7)	0 (0)	0 (0)	0 (0)	
Gastrointestinal disease	1 (1)	1 (7)	0 (0)	0 (0)	0 (0)	
Endocrine disease	11 (11)	0 (0)	1 (3)	10 (24)	0 (0)	
Cardiovascular disease	44 (44)	4 (27)	29 (97)	11 (26)	0 (0)	
Neurological disease	1 (1)	1 (7)	0 (0)	0 (0)	0 (0)	
Infectious disease	23 (23)	1 (7)	0 (0)	19 (45)	3 (25)	
Renal disease	8 (8)	7 (47)	0 (0)	1 (2)	0 (0)	
Musculoskeletal disease	9 (9)	0 (0)	0 (0)	1 (2)	8 (58)	
Other	1 (1)	0 (0)	0 (0)	0 (0)	1 (8)	

[a]Significant difference between Cardiology and Nephrology, Cardiology and Plastic Surgery, Endocrinology and Nephrology, Endocrinology and Plastic Surgery, and Nephrology and Plastic Surgery.
[b]Significant difference between Cardiology and Endocrinology and between Endocrinology and Plastic Surgery.
GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; OAD, oral antidiabetes drug.

insulin three times a day (45% of the total dose for breakfast bolus, 25% for lunch bolus, and 30% for dinner bolus). The total daily dose was adjusted by the treating physician during the ward round. Therefore the basal insulin was administered after the ward round at lunchtime.

The following safety features were implemented into the GlucoTab system: if a patient would not eat, basal insulin was administered, but the prescribed bolus insulin was withheld, and correctional bolus doses were administered for the regulation of particular BG values if required. The GlucoTab system also took into account the amount of bolus insulin that was still active in the patient's body from a previous dose (''insulin on-board''), by reducing bolus insulin by 25% per hour.[15] Another safety feature was to reduce the dose of basal insulin if the current basal dose injection was delayed. At any time, the healthcare professionals could overrule the suggested insulin dose and perform additional BG measurements.

At the beginning of the standardized glycemic management, a patient's preexisting antidiabetes therapy with glinides, sulfonylureas, and glitazones was stopped, and patients were assigned to receive standardized glycemic management according to the GlucoTab recommendations. Metformin and/or incretin-based therapies were maintained if there was no contraindication. At discharge, patients returned to their previous antidiabetes treatment, unless the treating physician prescribed continuing the insulin therapy performed during the study or changing to another insulin therapy.

All nurses and physicians were instructed on the study protocol, study-specific procedures, handling the GlucoTab system, and Good Clinical Practice before the start of the study. Healthcare professionals were invited to participate in a workshop about diabetes before study start and to fill out an usability questionnaire at the end of the study.

Capillary BG values were measured by using a point-of-care testing device (ACCU-CHEK® Inform system; Roche Diagnostics, Rotkreuz, Switzerland), which is integrated into the laboratory quality management system. Capillary BG measurements and insulin dosing were performed and documented by the nurse on duty.

CGM (iPro™2; Medtronic, Northridge, CA) data were available for a subset of 35 patients from 42 patients in total on the Endocrinology Ward; one patient lost the sensor, three patients had too few data points for analysis, and for another three patients no sensor transmitter was available. As CGM data were analyzed retrospectively, the treatment was not influenced by these data.

Statistical analysis

A sample size calculation was performed in order to test the study hypothesis by using a one-tailed one-sample *t* test weighted by the total number of BG measurements per subject, with a 5% level of significance and a power of 95%.

In order to test whether the mean percentage of BG measurements in the target range 70–140 mg/dL (primary outcome) was greater than the recent best-practice study with the criterion value of 42%,[12] we applied an one-tailed one-sample *t* test, weighted by the total number of BG measurements per subject. The level of significance was set to 5%.

The wards were compared by using the nonparametric Kruskal–Wallis rank sum test (metric variables) for analysis of secondary outcomes because patients were unequally distributed among the wards, with some table cells being unacceptably small for an analysis of variance. In case of a significant Kruskal–Wallis test, we performed pairwise comparisons by using the (nonparametric) Mann–Whitney U test. Fisher's exact test was used for nominal scales. No corrections for multiple testing were used, and the level of significance was set to 5% for all tests.

Finally, a multiple regression model to predict the mean daily BG value over all study days, except study Day 1, was fitted to the data. Study Day 1 was excluded because of incomplete datasets. Variables were sex, age, creatinine, hemoglobin A1c (HbA1c), body mass index, first total daily insulin dose per kilogram of body weight, diabetes duration, preexisting home insulin therapy at admission (yes, no), oral antidiabetes drugs at admission (yes, no), clinical ward, admission type (planned, acute), and the interaction between admission type and clinical ward. Model simplification was performed by using Akaike's information criterion. Statistical analysis was performed using R version 2.13.1 software.[16]

TABLE 2. EFFICACY, SAFETY, AND USABILITY OF THE GLUCOTAB SYSTEM ON DIFFERENT GENERAL WARDS

Variable	*Total* (n = *99*)	*Nephrology* (n = *15*)	*Cardiology* (n = *30*)	*Endocrinology* (n = *42*)	*Plastic surgery* (n = *12*)
Length of study (days)	7.8 ± 4.5	8.5 ± 5.4	6.8 ± 4.1	8.8 ± 4.4	5.9 ± 3.7
Implementation (%)					
Performance of expected					
BG measurement	95.2	92.4	97.2	94.8	98.4
Bolus insulin injections	94.2	96.8	97.4	93.2	86.5
Basal insulin injections	99.4	100	100	98.7	100
Adherence to					
Total daily insulin dose	97.5	98.5	97.5	98.0	92.9
Bolus dose suggestion	96.5	94.3	97.2	96.3	95.1
Basal insulin suggestion	96.7	91.1	96.3	96.8	91.0
Efficacy and safety					
BG (mg/dL)					
Mean daily	154 ± 35	162 ± 34	163 ± 33	150 ± 35	134 ± 31
Mean prebreakfast	147 ± 43	151 ± 38	156 ± 47	147 ± 44	119 ± 28
Mean prelunch	170 ± 54	197 ± 59	179 ± 58	163 ± 50	137 ± 36
Mean predinner	153 ± 41	141 ± 51	164 ± 40	146 ± 36	164 ± 42
Mean bedtime	153 ± 39	165 ± 41	164 ± 31	146 ± 39	136 ± 42
Pre-enrollment	188 ± 73	185 ± 43	173 ± 58	204 ± 88	158 ± 55
BG in target 70–140 mg/dL (%)[a]	50.2 ± 22.2	39.3 ± 13.7	40.7 ± 18.9	52.3 ± 20.7	64.9 ± 24.6
BG in different ranges (%)					
< 40 mg/dL	0.0	0.0	0.0	0.0	0.0
40 to <60 mg/dL	0.5	0.2	0.0	0.8	0.4
60 to <70 mg/dL	1.4	0.8	0.3	2.2	1.3
70 to <180 mg/dL	72.5	64.6	70.6	74.4	83.7
180 to <300 mg/dL	22.9	29.4	27.2	20.0	14.2
≥ 300 mg/dL	2.7	5.0	1.9	2.6	0.4
Antihyperglycemic therapy					
First calculated TDD (IU)[b]	38.9 ± 21.7	33.6 ± 11.3	33.5 ± 16.6	44.8 ± 27.5	38.3 ± 15.1
First TDD/kg of body weight (IU)	0.43 ± 0.19	0.36 ± 0.10	0.39 ± 0.11	0.49 ± 0.24	0.44 ± 0.14
Mean daily injected insulin dose during study (IU)					
Injected bolus insulin dose	28.5 ± 19.2	27.3 ± 14.9	25.8 ± 12.3	32.5 ± 25.1	21.0 ± 6.7
Injected basal insulin dose	22.9 ± 18.2	21.0 ± 7.6	17.8 ± 8.6	28.7 ± 25.0	17.1 ± 7.4
Concomitant drugs (*n*)					
Patients with OADs	36	2	13	14	7
Patients with GLP-1 analogs	6	0	2	4	0
Patients with steroids	4	1	1	1	1

[a]Primary end point. Significant differences occurred between Endocrinology and Cardiology ($P = 0.02$), Plastic Surgery and Nephrology ($P = 0.01$), Plastic Surgery and Cardiology ($P = 0.02$), and Nephrology and Endocrinology ($P = 0.01$).

[b]Total daily dose (TDD) might deviate from the injected total insulin dose of Day 1 depending on the time of day when a patient was started on GlucoTab therapy.

BG, blood glucose; GLP-1, glucagon-like peptide-1; IU, international units; OAD, oral antidiabetes drug.

Results

Implementation of standardized glycemic management

The standardized workflow support with the GlucoTab system was highly accepted by healthcare professionals on all participating clinical wards as indicated by the performance of the expected BG measurements and the adherence to insulin dose suggestions (Table 2).

In total, physicians adhered to the suggested total daily insulin doses in 97.5% of cases (Table 2 and Fig. 1), and nurses' adherence rates with suggested bolus insulin doses and basal insulin doses were 96.5% and 96.7%, respectively. If corrections were performed by healthcare professionals, the changes were relatively small: 0.7 ± 1.6 international inits (IU) for bolus insulin and 0.9 ± 2.8 IU for basal insulin.

Efficacy of standardized glycemic management

By using the GlucoTab system, the percentage of BG values in the target range increased over time in all participating clinical wards (Fig. 1). Overall, the mean percentage of BG measurements in the target range 70–140 mg/dL was 50.2 ± 22.2%, which was significantly higher than the criterion value of 42% deriving from a recent best-practice study ($P = 0.001$).[12] Of the patients, 72.2% had a reduction of the mean BG during hospital stay compared with the estimated BG based on HbA1c at admission.[17] In all patients with an estimated average BG of >200 mg/dL, based on the HbA1c, the mean BG during the study was improved (Fig. 1C). The overall mean of 2,466 BG measurements was 154 ± 35 mg/dL. Details of glycemic management across the clinical wards are shown in Table 2.

The percentage of BG in the target range 70–140 mg/dL was highest on the Plastic Surgery Ward (64.9 ± 24.6%). The lowest value was found on the Nephrology Ward (39.3 ± 13.7%). Analysis of the CGM data of patients on the Endocrinology Ward indicated that more than half of the study time (54.0%) subcutaneous BG values were in the target range of 70–140 mg/dL (Fig. 2) and confirmed that reference BG values were representative (52.3% in the target range; Table 2).

Although these observations suggest variations within glycemic management among the clinical wards, a regression analysis to predict the mean daily BG value showed that the

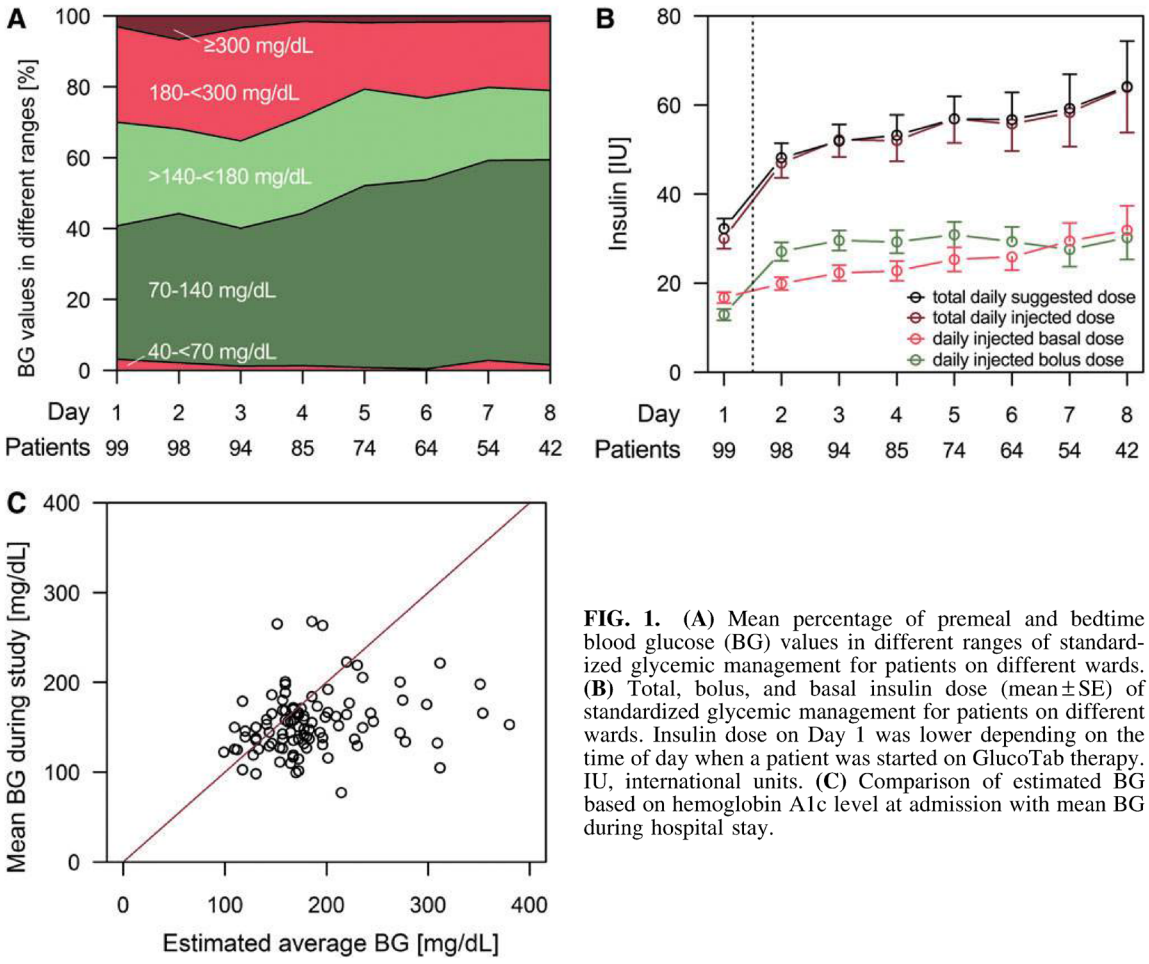

FIG. 1. **(A)** Mean percentage of premeal and bedtime blood glucose (BG) values in different ranges of standardized glycemic management for patients on different wards. **(B)** Total, bolus, and basal insulin dose (mean ± SE) of standardized glycemic management for patients on different wards. Insulin dose on Day 1 was lower depending on the time of day when a patient was started on GlucoTab therapy. IU, international units. **(C)** Comparison of estimated BG based on hemoglobin A1c level at admission with mean BG during hospital stay.

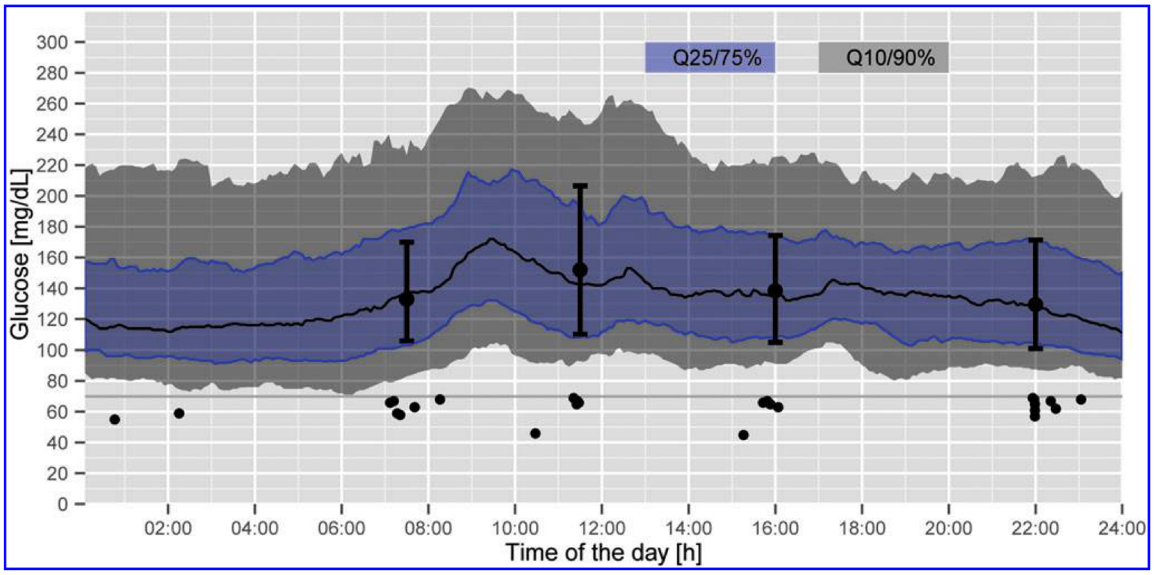

FIG. 2. Daily continuous glucose monitoring profiles and reference blood glucose values (black circles = reference blood glucose values) in 35 patients on the Endocrinology Ward. Q, quartile.

BG value was not affected by a specific clinical ward. Patients with preexisting home insulin therapy at admission had, on average, higher (+26 mg/dL) mean daily BG values during the standardized glycemic management than patients without preexisting home insulin therapy. Particularly on the Cardiology Ward the type of admission had a strong impact on the mean daily BG value. Acutely admitted patients on the Cardiology Ward had on average higher (+30 mg/dL) mean daily BG values than patients with acute admissions at the other wards (+4 mg/dL). Furthermore, the regression analysis showed that a higher first insulin dose per kilogram of body weight by 0.1 IU or a lower HbA1c value at admission by 10 mmol/mol was associated with a lower mean BG by 5 mg/dL and 4 mg/dL, respectively.

Safety of standardized glycemic management

The number of hypoglycemic events on the different wards using the GlucoTab system was comparable (Table 2). No severe hypoglycemic event below 40 mg/dL was observed. Of all measurements in the range 40 to <60 mg/dL, 0.5% occurred in nine different patients. Of the measurements in the range of 60 to <70 mg/dL, 1.4% occurred in 24 different patients. In patients on the Endocrinology Ward, the analysis of the CGM data confirmed a low risk for developing hypoglycemia: 0% and 1.2% for measurements in the ranges <40 mg/dL and 40 to <60 mg/dL, respectively (Fig. 2).

Twenty-eight mild and moderate adverse events and one serious adverse event (stent thrombosis) occurred. None of these events was recognized as related to the GlucoTab system.

Usability of standardized glycemic management

At the end of the study, 65 healthcare professionals completed a questionnaire (54 women and 11 men; mean age, 36 ± 11 years; 51 nurses, 14 physicians). Forty-two healthcare professionals had previous experience with the use of mobile devices. Fifty-nine healthcare professionals (91%) felt confident in performing glycemic management with the GlucoTab system. Fifty-eight healthcare professionals (89%) believed that the system was practical to use in daily clinical routine. Fifty-two participants (80%) stated that using GlucoTab could prevent medical errors associated with drug prescriptions. Fifty-six healthcare professionals (86%) answered that when using the system, physicians had to be consulted less often about glycemic management. Fifty-five healthcare professionals (85%) stated that glycemic control was more efficient when using the GlucoTab system. Different perceptions of workload were assessed. Thirteen healthcare professionals indicated a workload increase, 33 indicated a workload decrease, and 12 indicated no change in the workload, when using the GlucoTab system. Seven healthcare professionals did not answer this question.

Discussion

Our data indicate that standardized glycemic management guided by the GlucoTab system for workflow and decision support can be implemented efficiently and safely and is user-accepted in different wards in a tertiary-care hospital. Of the BG measurements, 50.2 ± 22.2% were in the target range (70–140 mg/dL) by using the GlucoTab. Moreover, the system was implemented without any occurrence of severe hypoglycemia and with a high acceptance rate among healthcare professionals.

The high number of BG measurements and insulin injections performed according to suggested standardized care showed that the GlucoTab system was highly accepted and continuously used by healthcare professionals and that it was able to successfully guide the glycemic management process. This was also confirmed by the user questionnaire and by the tight adherence of healthcare professionals to the suggested

insulin doses. Adherence of healthcare professionals was considerably higher than in previous studies.[18,19] Schnipper et al.[19] performed a study on computerized order sets and reported that 67% of the patients received an adequate initial dose of nutritional insulin and that in only 37% of the patients' insulin orders were changed.

In our study, differences regarding glycemic control among the wards were observed, although adherence rates to insulin dosing and BG measurement suggestions of the GlucoTab system were comparable on the participating clinical wards. However, a regression analysis revealed that ward assignment was not an appropriate variable to predict the mean BG value. In this analysis, an acute admission influenced the glycemic control on all wards, and the strongest influence of an acute admission on BG was found on the Cardiology Ward (+30 mg/dL). We assume that these findings may be related to myocardial infarction, which is the predominant diagnosis of acute admission on the Cardiology Ward and which is associated with local and systemic inflammation[20] leading to impaired glycemic control and possible linkage to poor cardiac outcome.[21]

According to our regression analysis, further modification of the basal bolus algorithm may be required for a more personalized care in the acute phase of cardiac events.

Higher mean BG measurements were observed not only on the Cardiology Ward, but also on the Nephrology Ward. It is surprising that the creatinine value did not influence the mean daily BG value according to the regression analysis. Thus, we assume that the lower first total daily insulin dose may be responsible for the less stringent glycemic control in patients on the Nephrology Ward. This lower first total insulin dose was a strong predictor for impaired glycemic control in the model. According to the algorithm design, the initial dose was reduced from 0.5 to 0.3 IU/kg of body weight if a creatinine value was >2 mg/dL. However, a recent randomized controlled trial in patients with a glomerular filtration rate of <45 mL/min showed that an insulin starting dose of 0.25 IU/kg of body weight did not worsen glycemic control when compared with the control group that used an insulin starting dose of 0.5 IU/kg of body weight. The authors speculated that in these patients the insulin resistance might be a key element of impaired glycemic control.[22]

According to the regression analysis, preexisting home insulin therapy and the HbA1c values in addition to the type of hospital admission and the first total daily insulin dose are essential factors that influence the mean BG values during hospitalization. Thus, these factors have the potential to be used for a more personalized algorithm.

In our study the risk of hypoglycemia was low. None of the BG values was below 40 mg/dL. Hypoglycemic events were evenly distributed among patients. The percentages of BG measurements in the different hypoglycemic ranges and in the target range were similar to those found in comparable studies.[11,12,23,24]

Several limitations of our study have to be addressed. The present study was a noncontrolled clinical study. However, a retrospective assessment of glycemic control on two wards participating in this study achieved 57% (Endocrinology) and 51% (Cardiology) in the range of 70–180 mg/dL in routine care. In addition, the results of a previously published prospective controlled study on these two wards showed that patients in a paper-based basal bolus algorithm group had a significantly higher percentage of BG measurements in the range of 70–180 mg/dL than patients in routine care group (73% vs. 53%). These data indicate that glycemic control was improved by the use of the GlucoTab system compared with routine care.[7,13]

Because of the competitive recruiting process, the number of included patients per ward differed considerably, and results from the different wards and the regression analysis can only be interpreted with caution. The implemented target range of less than 140 mg/dL for premeal BG measurements may have to be reconsidered for certain populations in hospital care. Modified algorithms (e.g., for geriatric patients with individualized target ranges[25]) need to be developed and evaluated.

In conclusion, our data demonstrate that the GlucoTab system allowed an efficacious, safe, and user-accepted implementation of standardized glycemic management in different general wards of a tertiary-care hospital. Consequently, the system can support healthcare professionals in improving glycemic management relying on evidence-based guidelines for non-critically ill hospitalized patients.

Acknowledgments

The authors acknowledge the critical review of the manuscript and the editorial assistance of B. Boulgaropoulos, Medical University of Graz, the data management of B. Tschapeller, C. Krainer (both from Joanneum Research GmbH), and G. Schwagerle, Medical University of Graz, the data monitoring of A. Berghofer, Medical University of Graz, the technical implementation of support and software testing of F. Chiarugi and D. Manousos, FORTH-ICS, and the mobile device security and user management of M. Enzmann and F. Franke, Fraunhofer SIT. The authors thank the nurses and physicians of the Divisions of Endocrinology and Metabolism, Cardiology, Nephrology, and Plastic Surgery, Medical University of Graz, for their contribution in the performance of the study. This study was performed within the REACTION project, which was funded by the European Commission under the 7th Framework Program in the area of Personal Health Systems under Grant Agreement Number 248590.

Author Disclosure Statement

T.R.P. is a member in the advisory board of NovoNordisk A/S, Eli Lilly, and Roche Diagnostics and has received speaker honoraria from NovoNordisk A/S, Eli Lilly, and AstraZeneca. J.K.M. is a member in the advisory board of Sanofi-Aventis Austria and has received speaker honoraria from NovoNordisk A/S and Roche Diagnostics. J.P. has received speaker honoraria from NovoNordisk A/S. K.M.N., B.H., F.A., K.D., T.A., L.S., S.S., P.B., F.M., C.S., A.R.R., D.B.L., and L.-P.K. declare no competing financial interests exist.

K.M.N., J.K.M., B.H., S.S., P.B., L.S., and J.P. designed and performed the study, interpreted data, and contributed to discussions. K.M.N. drafted the manuscript. T.A. and K.D. designed the study and performed statistical analysis. F.A., C.S., and D.B.L. performed the study. A.R.R., F.M.F., and L.-P.K. supervised the project. T.R.P. interpreted data, contributed to discussions, supervised the project, and is the guarantor of this work. All authors critically revised the article and approved the final version of the manuscript.

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2. Summary

The study reported in this chapter was the first application of GlucoTab® on more than one hospital ward. The aim of the clinical study was to investigate efficacy, safety and usability of the system which was used for glycemic management in non-critically ill T2DM patients. The overall patients' mean BG level was 154±35 mg/dL and 72.5% of BG measurements were within the accepted extended target range for analysis (70-180 mg/dL). Only 1.9% of BG measurements were below 70 mg/dL and these low glycemic events were evenly distributed in the patient population and did not occur clustered. There was no severe hypoglycemic episode below 40 mg/dL. The adherence to the insulin dosing decision support by HCPs was high (96.5% for bolus insulin, 96.7% for basal insulin). Also the adherence to the planned workflow was high which is reflected in the high performance of expected BG measurements and insulin injections.

Comparing the primary endpoint of the study ("% BG measurements in the range 70 to 140 mg/dL) revealed statistically significant differences between the study sites. To further investigate these differences, a multiple regression model to predict the mean daily BG value over all study days, except study day 1, was developed. Following predictor variables of the model had significant influence on the patients' mean daily BG:

- High HbA1c at admission was associated with higher mean daily BG
- Patients with preexisting home insulin therapy at admission had higher mean daily BG
- A higher first insulin TDD per kilogram body weight was associated with lower mean daily BG
- Type of admission (acute or planned) had a significant influence on mean daily BG

Patients with preexisting home insulin therapy had on average higher (+26 mg/dL) mean daily BG values, than patients without preexisting home insulin therapy. Particularly on the Cardiology ward, the type of admission had a strong impact on the mean daily BG. Acutely admitted patients on the Cardiology ward had on average higher mean daily BG values (+30 mg/dL) than patients with acute admissions at the other wards (only +4 mg/dL). A 0.1 IU higher first insulin dose per kilogram of body weight was associated with a 5 mg/dL lower mean daily BG level, and a 10 mmol/mol lower HbA1c value at admission was associated with a 4 mg/dL lower mean daily BG level. Surprisingly, renal function estimated by the patients' serum creatinine level did not influence the model, even though the laboratory parameter is used in the calculation of the patients' initial TDD. In patients with a serum

creatinine level above or equal 2 mg/dL the initial TDD is decreased. It was assumed that the lower first total daily insulin dose in patients on the Nephrology ward may be responsible for the higher mean daily BG levels.

Subgroup analyses revealed that although mean daily BG was higher for some patient subgroups, the occurrence of BG values below 70 mg/dL was comparable in all subgroups. The insulin dosing algorithm in its current form was safe in all patient subgroups, but was not equally effective for all patients.

CHAPTER VI

Clinical benefit of computerized workflow and decision support

This chapter presents the findings of a previously published article (**Donsa** et al. 2016 [58]). In this post-hoc analysis a comparison of error rates was performed when using a paper-based and a computerized way of clinical decision and workflow support. Furthermore, this chapter elaborates on clinical benefits of using computerized workflow and decision support.

1. Impact of errors in paper-based and computerized diabetes management with decision support for hospitalized patients with type 2 diabetes. A post-hoc analysis of a before and after study [Donsa et al. 2016]

International Journal of Medical Informatics 90 (2016) 58–67

Contents lists available at ScienceDirect

International Journal of Medical Informatics

journal homepage: www.ijmijournal.com

Impact of errors in paper-based and computerized diabetes management with decision support for hospitalized patients with type 2 diabetes. A post-hoc analysis of a before and after study

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 18 March 2016
Accepted 22 March 2016

Keywords:
Clinical decision support
Medication management system
Medication order entry
Medication errors
Type 2 diabetes mellitus
Basal-bolus insulin therapy
Best practice

ABSTRACT

Objective: Most preventable adverse drug events and medication errors occur during medication ordering. Medication order entry and clinical decision support are available on paper or as computerized systems. In this post-hoc analysis we investigated frequency and clinical impact of blood glucose (BG) documentation- and user-related calculation errors as well as workflow deviations in diabetes management. We aimed to compare a paper-based protocol to a computerized medication management system combined with clinical workflow and decision support.

Methods: Seventy-nine hospitalized patients with type 2 diabetes mellitus were treated with an algorithm driven basal-bolus insulin regimen. BG measurements, which were the basis for insulin dose calculations, were manually entered either into the paper-based workflow protocol (PaperG: 37 patients) or into GlucoTab®—a mobile tablet PC based system (CompG: 42 patients). We used BG values from the laboratory information system as a reference. A workflow simulator was used to determine user calculation errors as well as workflow deviations and to estimate the effect of errors on insulin doses. The clinical impact of insulin dosing errors and workflow deviations on hypo- and hyperglycemia was investigated.

Results: The BG documentation error rate was similar for PaperG (4.9%) and CompG group (4.0%). In PaperG group, 11.1% of manual insulin dose calculations were erroneous and the odds ratio (OR) of a hypoglycemic event following an insulin dosing error was 3.1 (95% CI: 1.4–6.8). The number of BG values influenced by insulin dosing errors was eightfold higher than in the CompG group. In the CompG group, workflow deviations occurred in 5.0% of the tasks which led to an increased likelihood of hyperglycemia, OR 2.2 (95% CI: 1.1–4.6).

Discussion: Manual insulin dose calculations were the major source of error and had a particularly strong influence on hypoglycemia. By using GlucoTab®, user calculation errors were entirely excluded. The immediate availability and automated handling of BG values from medical devices directly at the point of care has a high potential to reduce errors. Computerized systems facilitate the safe use of more complex insulin dosing algorithms without compromising usability. In CompG group, missed or delayed tasks had a significant effect on hyperglycemia, while in PaperG group insufficient precision of documentation times limited analysis. The use of old BG measurements was clinically less relevant.

Conclusion: Insulin dosing errors and workflow deviations led to measurable changes in clinical outcome. Diabetes management systems including decision support should address nurses as well as physicians in a computerized way. Our analysis shows that such systems reduce the frequency of errors and therefore decrease the probability of hypo- and hyperglycemia.

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http://dx.doi.org/10.1016/j.ijmedinf.2016.03.007
1386-5056/

1. Introduction

Most preventable adverse drug events and medication errors are related to the medication process itself and mainly occur during ordering [1–3]. Computerized systems (medication order entry, patient data management) are cost effective [4], significantly reduce prescribing errors [5–8] and charting time [9]. Additionally, clinical decision support systems (CDSS) support calculation of drug doses and management of the increasing number of drugs, treatment regimens and side effects. The combination of medication order entry systems and CDSS reduces medication errors [5] and their use has also been recommended for diabetes therapy in hospitalized patients [10–13].

Around 20% of hospital inpatient days occur in diabetes patients who have an increased risk to experience adverse events during hospital stay [13–15]. An improvement in diabetes management results in lower rates of hospital complications in general medicine and surgery wards [16,17]. But a recent diabetes inpatient audit showed that 37% of diabetes patients experienced at least one diabetes medication error during hospitalization and that these patients were more than twice as likely to experience severe hypoglycemia [18]. International diabetes experts recommend a structured approach and an algorithm-driven basal-bolus insulin regimen for hospitalized type 2 diabetes mellitus (T2DM) patients [19]. This regimen involves long acting insulin to supplement basal insulin requirements during periods of fasting and separate injections of rapid acting insulin to prevent rises in blood glucose (BG) levels resulting from meals. Diabetes management requires complex and interdisciplinary cooperation of health care professionals (HCPs) involving ordering doses and correction schemes, BG measurement and timely administration of resulting insulin doses. Clear evidence that the combination of computerized medication order entry systems and CDSS reduces clinical adverse drug events is still missing [5].

We have integrated a customized version of a previously published algorithm for basal-bolus insulin therapy in T2DM patients [20–22] into the workflow of a general internal medicine ward. We first tested the basal-bolus insulin regimen in a paper-based version of a medication management protocol with insulin dosing decision support [23]. In a second step, the algorithm was refined and implemented in a computerized workflow and decision support system which was additionally tested in a clinical study on 4 different wards [24].

In the present post-hoc analysis we aimed to determine the frequency and clinical impact of blood glucose (BG) documentation-, user-related calculation errors and workflow deviations in diabetes management. We compared the paper-based protocol to the computerized medication management system including clinical workflow and decision support. The data collected in the clinical studies was analyzed to describe errors. To further analyze clinical impact of these errors a workflow simulator was used to estimate their effect on insulin doses.

2. Methods

2.1. Study design and patient characteristics

We used a subset of data (one ward) from two previously published clinical studies [23,24]. Both studies were conducted at the general ward of the Division of Endocrinology and Metabolism at the Department of Internal Medicine (Medical University of Graz, Austria). On this ward additional continuous glucose monitoring (CGM) was performed in both clinical studies. Both studies were approved by the local ethics committee and performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Adult patients (≥18 years of age) with T2DM who were treated with diet alone and/or with any oral or injectable antihyperglycemic therapy and who were admitted to the general ward were included in the study. The study ended with hospital discharge, the transfer of the patient to a different ward, or after 21 treatment days.

For the post-hoc analysis we used a before and after study design: First, diabetes management was performed using a paper-based protocol for an algorithm driven basal-bolus insulin therapy from July 2011 to April 2012, (PaperG group). After 12 month of using routine care diabetes management to unlearn the procedures of the algorithm driven basal-bolus insulin therapy, diabetes management was conducted using a computerized system from May 2013 to December 2013, (CompG group). The paper-based protocol and the computerized system for medication management were specifically designed to support basal-bolus insulin therapy of T2DM patients. Both methods comprise the following functionalities which aid physicians and nurses: 1) medication order entry with insulin dosing decision support for physicians, 2) workflow management for physicians and nurses, 3) data entry at the bedside and 4) drug administration support including insulin dose calculation for nurses.

This study included data from 79 T2DM patients. BG measurements were entered manually, either into a paper-based workflow and medication management protocol (PaperG: 37 patients) or into GlucoTab®—a mobile Android tablet PC based system (CompG: 42 patients). The true measured BG values and measurement times were retrospectively extracted for both groups from the Laboratory Information System (LIS) and compared with the manually entered data. Insulin dose calculations were performed manually in the PaperG group and with GlucoTab® in the CompG group. In both groups, the users were trained in the correct use of the protocol/system and the insulin dosing algorithm. HCPs were unaware of the fact that medication errors were investigated.

2.2. Clinical workflow and insulin dosing algorithm

In both groups, dosing decisions were based on four daily capillary BG finger-stick measurements (three pre-meal and one bedtime measurement). Additional measurements were performed if deemed necessary by the HCPs. The algorithm was used to calculate the initial total daily dose (TDD) of insulin based on patient weight, age and renal function as well as to calculate a new TDD for the next 24 h based on the previous TDD and BG values of the preceding 24 h. The calculated TDD was either accepted or modified by the physicians and the ordered TDD was divided into 50% daily basal and 50% daily bolus insulin dose. The bolus dose was distributed among the three meals (breakfast, lunch, dinner). If pre-meal BG values were below the target range, the insulin bolus was reduced whereas BG values above the target range induced an increased bolus dose. The basal-bolus insulin algorithm aims for fasting and pre-meal BG levels of 100–140 mg/dL. In case of additional insulin suggested due to high BG, the algorithm further adjusted the dose using an insulin sensitivity parameter. Insulin sensitivity (sensitive, normal and resistant) was assessed by the attending physician during each morning round. Additional bolus injections were performed if deemed necessary by the HCPs. Authorized nurses were able to modify the suggestion of the decision support algorithm and after confirmation of the suggested insulin dose the insulin was injected subcutaneously. The underlying workflow and the sequence of operations of the used algorithm driven basal-bolus insulin regimen were identical in both groups (Fig. 1).

Paper-based workflow and decision support (PaperG group)

The use of the insulin dosing algorithm requires only basic arithmetic operations and HCPs were trained in the correct use. BG

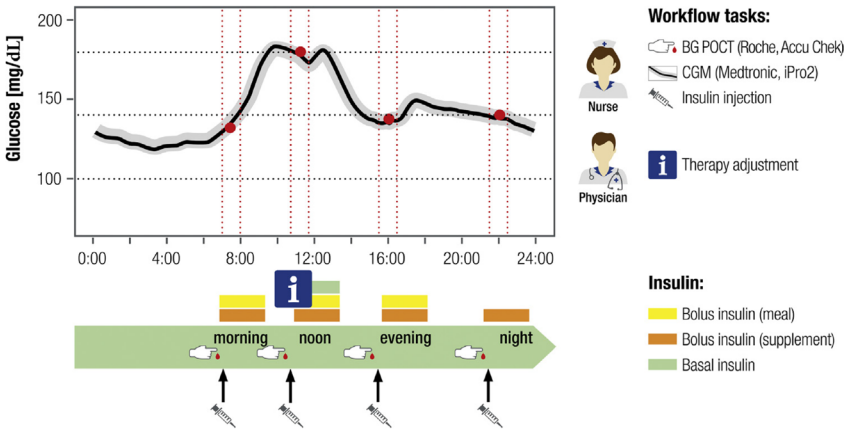

Fig. 1. Interdisciplinary clinical workflow for diabetes management in the hospital using basal-bolus insulin therapy.

Table 1
Patient characteristics.

Variable	Total (n = 79)	PaperG (n = 37) [23]	CompG (n = 42) [24]	*p*
Gender, female (n/%)	31/39.2%	11/29.7%	20/47.6%	0.024*
Race: caucasian/other (n)	77/2	35/2	42/0	0.127
Age (years)	68 ± 11	70 ± 12	67 ± 11	0.277
Body Mass Index (kg/m^2)	30.4 ± 6.8	29.7 ± 6.8	31.1 ± 6.8	0.615
Serum creatinine (mg/dL)	1.5 ± 1.0	1.5 ± 0.5	1.6 ± 1.3	0.572
HbA1c				
mmol/mol	73 ± 27	76 ± 7	70 ± 24	0.407
%	8.8 ± 4.6	9.1 ± 2.8	8.6 ± 4.4	
Diabetes duration (years)	15 ± 11	14 ± 12	15 ± 10	0.523
Pre-admission diabetes therapy (n)				
Diet only	7	5	2	>0.05
OAD only	20	12	8	
Insulin only	42	18	24	
Combination therapy	10	2	8	
Admission diagnosis (n)				
Endocrine disease	19	9	10	>0.05
Cardiovascular disease	25	14	11	
Infectious disease	28	9	19	
Other	7	5	2	
Patients with CGM (n)	67	32[a]	35[b]	
Length of study (days)	8.2 ± 4.5	7.5 ± 4.6	8.8 ± 4.4	0.201

[a] 2 of the 5 patients without CGM data were not willing to use CGM, 2 patients lacked sufficient subcutaneous adipose tissue and 1 patient lost the sensor during the study period.
[b] 1 patient lost the sensor, 3 patients had too few data for analysis and for another 3 patients no sensor transmitter was available.
* Statistically significant difference ($p < 0.05$).

values, calculated and accepted insulin doses were recorded in the paper-based diabetes management protocol [23].

To calculate insulin bolus doses, nurses had to consult a correction scheme and consequently execute additions or subtractions. To calculate the TDD, physicians had to calculate percentage increase or decrease of a previous TDD. Calculation of the initial TDD required multiplications, divisions and ratios [23]. HCPs were equipped with pocket calculators to calculate insulin doses.

GlucoTab®—computerized workflow and decision support (CompG group)

GlucoTab® (Joanneum Research GmbH and Medical University of Graz, both Graz, Austria) is a mobile computerized client-server clinical workflow and decision support system supporting HCPs in diabetes management of hospitalized T2DM patients directly at the point of care. The client is connected over the hospital WiFi to the GlucoTab® server which has a HL7 interface to receive hospital patient master data. It assists in organizing the treatment workflow by providing automated workflow support, including display for open tasks, facilitating documentation and providing visualization of BG values, nutrition and insulin doses. The main function of the system is the provision of insulin dose recommendations for basal-bolus insulin treatment of T2DM patients. GlucoTab® is a CE marked medical device software [24].

Although additional safety features have been implemented in the computerized version of the algorithm for insulin dosing, the underlying workflow and the sequence of operations were identical between the two groups. GlucoTab® also takes into account the amount of insulin that is still active in the patient's body from a previous dose ('Insulin on Board'). Another additional feature is the reduction of the basal insulin dose for delayed basal insulin administrations. Furthermore, the rules to calculate therapy adjustments were slightly altered in the CompG group, leading to a more dynamic therapy adjustment.

Glucose measurements

Measurements were conducted using a Point of Care Testing (POCT) device (Roche Accu-Chek® Inform System, Roche Diagnos-

Table 2
Detection of errors and their frequency.

	PaperG	CompG
All BG values: (n)	1042	1337
Correct match: (n/%)	972 (93.3%)	1265 (94.6%)
Automated match	913 (87.6%)	1257 (94.0%)
Manual match	59 (5.7%)	8 (0.6%)
No Match: (n/%)	19 (1.8%)	19 (1.4%)
BG documentation errors (incorrect match): (n/%)	51 (4.9%)	53 (4.0%)
Average absolute error ± SD (mg/dL)	6.8 ± 12.2	12.2 ± 21.4
Median absolute error and range (mg/dL)	3 (1–64)	3 (1–100)
Workflow deviations [a]:	0.9%	5.0%
Missed BG measurements [b]	1/796 (0.1%)	52/1156 (4.5%)
Missed bolus insulin injections [b]	1/597 (0.2%)	49/867 (5.7%)
Missed therapy adjustments/basal injections	12/247 (4.9%)	19/367 (5.2%)
Insulin dose calculations with old BG measurements (older than 30 min): (n/%)	n/a	231/1251 (18.5%)
Average time lag ± SD (min)	n/a	48.8 ± 21.6
Median lag and range (min)	n/a	42.8 (30.0–230.5)
User calculation errors:	11.1%	0.0%
All simulated calculations:	1190	1648
Bolus insulin calculations	98/943 (10.4%)	0/1251 (0.0%)
Daily insulin dose adjustments (basal insulin calculations)	29/210 (13.8%)	0/325 (0.0%)
Initial total daily insulin dose calculation	5/37 (13.5%)	0/42 (0.0%)

[a] Not comparable between groups.
[b] Excluding first and last study day.

tics, Switzerland) which automatically transmitted the BG values and measurement times to the LIS via a data interface. Data could not be made available in a timely manner through this interface for therapy. Therefore, manual data entry into the GlucoTab® was also required in the CompG group.

To present the complete pattern of daily BG levels, glucose was additionally monitored with CGM (iPro®2 system; Medtronic Minimed, Northridge, CA) [25]. CGM was only temporarily discontinued when patients had to undergo certain diagnostic procedures. CGM data were calibrated retrospectively based on the four daily BG measurements.

The target range for the insulin-dosing algorithm was defined in the range of 100–140 mg/dL. A recommended extended target range from 70 to 180 mg/dL was used for analysis [19,20,23]. Hypoglycemia was defined as glucose values <70 mg/dL and hyperglycemia >250 mg/dL.

2.3. Data processing and analysis

In our analysis we: A.) detected the number and frequency of errors, B.) investigated the effect of BG documentation errors and user calculation errors on insulin dose calculation, and C.) investigated the clinical impact of insulin dosing errors and workflow deviations. The complete structure of data processing and analysis is shown in Fig. 2.

We investigated the following types of errors:

BG documentation errors: occurred during the manual transfer of BG values from the POCT device to the diabetes management protocol/system and also include the use of *old BG measurements* for insulin dose calculations. An old BG measurement was defined as a BG measurement older than 30 min which was used for the calculation of an insulin dose. The computerized system allowed a maximum time difference of 30 min from BG measurement data entry to insulin dose calculation. 30 min were derived from clinical experience and based on a previous study [26]. Analysis of old BG measurements could only be performed in the CompG group.

User calculation errors: occurred during calculation of insulin doses. These include calculation of bolus and basal insulin and therapy initializations and adjustments of the TDD.

Workflow deviations: included missed tasks or tasks not performed on time. This was the case for BG measurements, insulin injections and therapy adjustments.

A. Detection of errors

To determine if BG documentation errors occurred, BG values from the LIS were matched with the corresponding manually entered values (step A.1). User calculation errors and workflow deviations were determined by using a workflow simulator (step A.2). The frequency of BG documentation errors, user calculation errors and workflow deviations was investigated in both groups. For a correct analysis of workflow deviations we included only full treatment days.

A.1. BG data matching

BG data matching was performed to retrieve the correct BG value and time of measurements from the POCT devices. The BG measurements stored in the LIS were matched with the data entered in the paper-based protocol and computerized system. Matching of the BG values was performed in an automated and in a manual step. Due to a lack of precision of documentation times in the PaperG group, slightly different matching criteria were used for the paper-based and computerized sources.

We defined the following cases by using matching criteria derived in cooperation with HCPs:

- *Correct automated match*: if BG value entry exactly equals LIS value and if time difference meets the match criteria.
  - PaperG group: time differences from data entry to correctly recorded entry in the LIS were allowed between −30 and 90 min (negative differences resulted from rounding to next full hour by the HCPs).

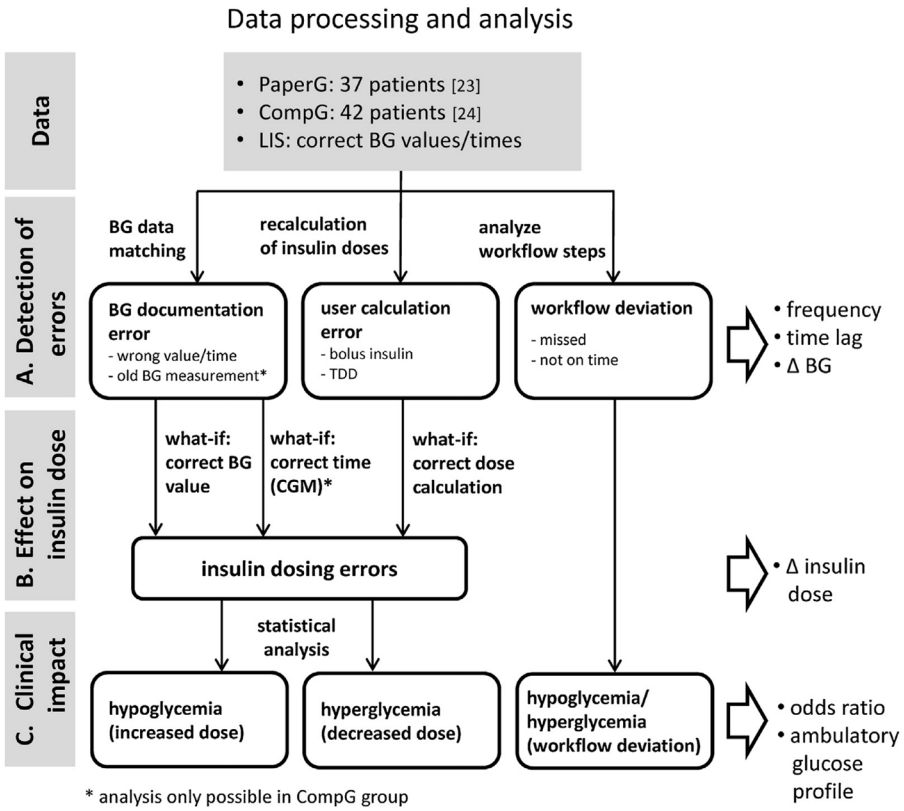

Fig. 2. Data processing and analysis (workflow chart).

- CompG group: only positive time differences smaller than 90 min were allowed.

- *Correct manual match*: if BG value entry exactly equals LIS value but the time difference does not meet the match criteria and no other BG measurements were performed in the interval.
- *No match*: if no corresponding value was found in the LIS due to inaccessible BG measurement values e.g. use of the patients personal glucometer instead of POCT device, problems with the POCT device.
- BG *documentation errors (incorrect match)*:
  - If BG values deviate (Δ BG) and time difference meets the match criteria.
  - If BG values deviate but time difference doesn't meet the match criteria and no other BG measurements were performed in this interval.

A.2. Workflow simulator—recalculation of insulin doses

The workflow simulator uses original GlucoTab® server software components which were developed and tested according to regulatory requirements for medical device software [27]. Recalculations were performed with the workflow simulator for all insulin dose decision support steps provided to HCPs to compare all manually entered data to an automatically calculated reference value. Firstly, the simulator was used to determine the frequency and amount of user calculation errors. Secondly, the simulator was used to retrace the original workflow and to recalculate insulin doses and therapy adjustments based on correct BG values and times.

B. Effect on insulin dose

Using the identified erroneous BG documentations and user calculation errors, we investigated their effect on insulin dose calculations (insulin dosing errors). In a what-if analysis performed with the workflow simulator, the frequency and amount of change of insulin doses (Δ insulin dose) was determined for both groups. For BG documentation errors, recalculations were performed using the correct measurement values from the LIS. For old BG measurements, the glucose levels at the time of insulin dose calculation (obtained by CGM) were used for the recalculation of insulin doses.

C. Clinical impact

C.1. Insulin dosing errors

Only errors resulting in changes of insulin doses were considered in the impact analysis. If two independent errors led to a correct insulin dose by coincidence, this error was excluded from the impact analysis. We investigated the impact of errors on subsequent BG levels by calculating the odds ratio (OR) of hypoglycemia and hyperglycemia after insulin dosing errors. We used insulin dosing errors leading to increased insulin doses for calculation of the impact on hypoglycemia and insulin dosing errors leading to decreased insulin doses in case of hyperglycemia. Modifications of the decision support suggestions by HCPs were accounted for in the impact analysis but not considered as errors. Insulin dosing errors affecting long acting insulin doses were considered to have an impact for 24 h on the patients' BG levels. This was the case for insulin dosing errors affecting therapy adjustments, ther-

Table 3
Effect on insulin dose.

BG documentation errors affecting insulin dose calculations	PaperG	CompG
Bolus insulin calculations (errors/calculations) (%)	5/45 (11.1%)	11/46 (23.9%)
Average absolute error ± SD (IU)	2 ± 1.4	3.4 ± 2.0
Median absolute error and range (IU)	2 (2–4)	4 (2–8)
Median absolute error and range/TDD (%)	5.6 (3.6–9.5)	5.3 (1.3–16.7)
Maximum additionally ordered (IU; IU/TDD)	2; 5.6%	8; 13.6%
Maximum withheld (IU; IU/TDD)	4; 9.5%	4; 16.7%
Daily insulin dose adjustments (basal insulin calculations)	0/51 (0.0%)	8/53 (15.1%)
Average absolute error ± SD (IU)	–	4.8 ± 2.9
Median absolute error and range (IU)	–	3.5 (1–9)
Median absolute error and range/TDD (%)	–	8.0 (5–26.9)
Maximum additionally ordered (IU; IU/TDD)	–	9; 15.8%
Maximum withheld (IU; IU/TDD)	–	7; 26.9%
Old BG measurements affecting insulin dose calculations [a]		
Bolus insulin calculations	n/a	41/157 (26.1%)
Average absolute error ± SD (IU)	n/a	5.3 ± 7.2
Median absolute error and range (IU)	n/a	3 (1–35)
Median absolute error and range/TDD (%)	n/a	8.2 (0.6–25.0)
Maximum additionally ordered (IU; IU/TDD)	n/a	35; 25.0%
Maximum withheld (IU; IU/TDD)	n/a	30; 16.7%
Daily insulin dose adjustments (basal insulin calculations)	n/a	10/157 (6.4%)
Average absolute error ± SD (IU)	n/a	4.6 ± 2.0
Median absolute error and range (IU)	n/a	4 (2–8)
Median absolute error and range/TDD (%)	n/a	8.7 (6.9–26.7)
Maximum additionally ordered (IU; IU/TDD)	n/a	8; 26.7%
Maximum withheld (IU; IU/TDD)	n/a	8; 9.2%
User calculation errors affecting insulin dose	11.1%	0.0%
Bolus insulin calculations	98/943 (10.4%)	0/1251 (0.0%)
Average absolute error ± SD (IU)	2.2 ± 1.4	–
Median absolute error and range (IU)	2 (1–8)5.6	–
Median absolute error and range/TDD (%)	(0.8–27.3)	–
Maximum additionally ordered (IU; IU/TDD)	5; 17.4%	–
Maximum withheld (IU; IU/TDD)	8; 27.3%	–
Total daily insulin dose calculation	34/247 (13.8%)	0/367 (0.0%)
Average absolute error ± SD (IU)	7.7 ± 12.0	–
Median absolute error and range (IU)	2.5 (1–58)	–
Median absolute error and range/TDD (%)	8.3 (1.1–49.2)	–
Maximum additionally ordered (IU; IU/TDD)	58; 49.2%	–
Maximum withheld (IU; IU/TDD)	31; 25.6%	–

[a] Not comparable between groups.

apy initializations and basal insulin administrations. Insulin dosing errors affecting rapid acting insulin doses were considered to have an impact until the next standard measurement interval (maximum 5 h). These were insulin dosing errors affecting bolus insulin injections and therapy adjustments.

C.2. Workflow deviations

The effect of missed or not on time performed insulin injections and the effect of the use of old BG measurements on subsequent hypo- and hyperglycemia was investigated.

2.4. Statistical analysis

Glucose profiles were analyzed based on recommendations for standardizing analysis and presentation of glucose monitoring data (ambulatory glucose profile) [28]. Glucose variability was calculated either as standard deviation (SD) or as coefficient of variation (CV) (SD/mean) × 100 of the BG data. For the ambulatory glucose profile, BG values in different ranges was defined as '% of BG readings' within a well-defined range e.g. 100–140 mg/dL. Errors are expressed as mean absolute values with SD and as median absolute errors with the corresponding range. In addition, insulin dosing errors are related to the patients' current TDD. This relative error indicates potential patient hazard. For example an increase of an insulin dose by 5 insulin units (IU) in a patient with a TDD of 20 IU is proportionally larger and more dangerous than in a patient with a TDD of 50 IU.

In the clinical impact analysis the effect size for the strength of association is reported as OR for hypo or hyperglycemic events following an error. The OR expresses odds in favor of hypo- or hyperglycemic events relative to odds in favor of euglycemic events.

Pearson's χ^2 test was used to analyze nominal data. Fisher's exact test was computed when a Table had a cell with an expected frequency of <5. Prior to data analysis, all metric outcome variables were checked for normality by means of a Shapiro–Wilk's test. Nonparametric tests (unpaired Wilcoxon's signed-rank test) were applied if the metric variables were not distributed normally. We used unpaired *t*-tests in case of normal distribution and variance homogeneity. Confidence interval (CI) is given at 95% and *p*-values less than 0.05 were deemed significant. Statistical analysis was performed using R-Statistics version 3.0.1 software [29].

3. Results

We included 2379 BG values and 2838 dosing decisions from 79 patients into data analysis. Except for gender, there were no statistically significant differences in the baseline characteristics between PaperG and CompG group (Table 1). We matched 98.2% (PaperG) and 98.6% (CompG) of the patients' BG values. The automated match process with electronic entries resulted in notably more matches in the CompG group (Table 2).

Table 4
Clinical impact: Hypo- or hyperglycemic events following different types of errors.

Type of error	Odds ratio	
	Hypoglycemia	Hyperglycemia
PaperG:		
Insulin dosing errors	3.1[a] (95% CI: 1.4–6.9)	0.4 (95% CI: 0.1–1.6)
Workflow deviations [b]	1.5 (95% CI: 0.4–6.5)	0.8 (95% CI: 0.2–4.4)
CompG:		
Insulin dosing errors	–[c]	1.6 (95% CI: 0.2–12.9)
Old BG measurements (what-if)	–[c]	0.8 (95% CI: 0.1–6.0)
Workflow deviations	1.1 (95% CI: 0.3–4.7)	2.2[a] (95% CI: 1.1–4.6)
Old BG measurements	1.0 (95% CI: 0.4–2.4)	1.1 (95% CI: 0.7–1.9)

[a] Statistically significantly different from 1.
[b] Lack of precision of documentation time.
[c] One cell of the contingency Table was 0.

A. Detection of errors

The number of BG documentation errors and the median absolute error were similar in both groups ($p > 0.2$). 64.7% (PaperG) and 43.4% (CompG) of BG values with documentation error were documented as too high.

In the CompG group we detected 5% workflow deviations and 18.5% of BG measurements used for dose calculations were older than 30 min.

B. Effect on insulin dose

88.2% (PaperG) and 86.8% (CompG) of BG measurements with documentation errors were used to calculate bolus insulin doses (Table 3). The remaining BG measurements were additional control measurements not used for dose calculations. Only 11.1% (PaperG) and 23.9% (CompG) of the BG documentation errors affected the results of bolus insulin dose calculations. The median absolute insulin dosing error was 2 IU (PaperG) and 4 IU (CompG).

In the CompG group CGM data was available for 157 out of 231 old BG measurements which were used for bolus calculations. The use of old BG measurements affected 41 bolus dose calculations and 10 daily dose adjustments with basal dose calculation. Up to 35 IU were additionally ordered and up to 30 IU were withheld due to insulin dose calculations using an old BG measurement.

In the PaperG group 11.1% user calculation errors were detected. The average absolute user calculation error for bolus doses was 2.2 ± 1.4 IU. User calculation errors having an impact for 24 h on the patients' BG levels resulted in an average absolute insulin dosing error of 7.7 ± 12.0 IU (TDD). Up to 58 IU (TDD) per day were additionally ordered due to user calculation errors. Recalculation of insulin doses in the CompG group using the workflow simulator confirmed correctness of all insulin doses calculated by GlucoTab®.

C. Clinical impact

In the PaperG group, insulin dosing errors had a statistically significant influence on hypoglycemia but not on hyperglycemia (Table 4). In the CompG group, no statistically significant effect of insulin dosing errors on hypo- or hyperglycemia was observed, probably due to the rare occurrence of these events. We observed no statistically significant relationship with hypo- or hyperglycemia in the what-if analysis, when using the correct glucose values from CGM in old BG measurements used for insulin dose calculations.

In the CompG group we observed a statistically significant relationship with workflow deviations only for hyperglycemia. The fact that 18.5% of the BG measurements used for insulin dose calculations were older than 30 min had no statistically significant effect on hypo- or hyperglycemia.

8 times more BG measurements (23.0% PaperG vs. 2.9% CompG) and 3 times more patients (89.2% vs. 28.6%) were influenced by insulin dosing errors in the PaperG group. Overall, the mean BG was similar in the PaperG and CompG group, ($p = 0.763$). The rate of hypoglycemic events was low in both groups (Table 5).

In the PaperG group 89.2% of the patients experienced at least one insulin dosing error. BG values affected by insulin dosing errors were more likely in the hypoglycemic range, 5.1% vs 2.8% ($p = 0.082$).

In the CompG group 57% of the patients experienced insulin dosing errors or workflow deviations. Insulin dosing errors and workflow deviations caused a significantly higher number of BG values in the hyperglycemic range ($p = 0.017$) and led to an increase of mean BG ($p = 0.058$) and a larger glycemic variability expressed as CV.

4. Discussion

In the PaperG group we detected 8 times more BG values and 3 times more patients that were influenced by insulin dosing errors compared to the CompG group. Manual dose calculations were the major source of insulin dosing errors and had a particularly strong influence on hypoglycemia in the PaperG group where the OR of hypoglycemic events following insulin dosing errors was 3.1 (95% CI: 1.4–6.8). Even though the dosing algorithm was simple, 11.1% of the calculations performed by HCPs were erroneous. Up to 49.2% of the TDD was additionally ordered and up to 27.3% of the TDD was withheld due to previous user calculation error.

The paper-based insulin-dosing algorithm was prone to error despite a highly standardized environment on a general ward with users trained in medication order entry and decision support. The majority of insulin dosing errors could have been easily prevented by implementing computerized insulin dose calculation. It is likely that the frequency of insulin dosing errors would have been even higher if our investigation was performed in standard hospital conditions. The high frequency of user calculation errors suggests that advanced insulin dosing algorithms should only be used with computerized decision support systems.

The rate of BG documentation errors was comparable in both groups, and even though these errors rarely affected insulin dose calculations, errors ranged up to 100 mg/dL in the CompG group. As a scroll wheel was used to enter BG values, we assume that the major source of the error were values that were falsely remembered or temporarily falsely noted during manual transfer. The absence of instant automated transfer of BG measurements from POCT BG meters to GlucoTab® presents a potential risk. Together with hospital staff and the manufacturer we will search for a way to provide BG values in a timely manner because immediate availability and automated handling of BG values directly at the point of care can eliminate these errors.

One reason for the larger average absolute insulin dosing error in the CompG group may be the use of a mobile tablet device for BG documentation whereas in the PaperG group BG values were recorded in case report forms as part of the clinical study documentation. In the CompG group routine BG documentation probably influenced the average absolute BG documentation error which had an impact on the frequency and amount of insulin dosing errors. Additionally, a more dynamic adjustment of the TDD was partly responsible for a higher number of affected insulin dose calculations in the CompG group.

Only the data provided by GlucoTab® and the workflow simulator allowed us to take a closer look at clinical workflows and to investigate the clinical impact of workflow deviations. The OR of a hyperglycemic event following a workflow deviation was 2.2 (95% CI: 1.1–4.6), probably because the majority of workflow devi-

Table 5
Ambulatory glucose profile: glucose values in different ranges.

	PaperG			CompG		
	All	No error	Error[a]	All	No error	Error[b]
Glucose values (n)	1023	788	235	1318	1208	110
Patients (n)	37	36	33	42	42	24
Mean BG (mg/dL)	147.2	148.3	143.5	149.1	147.9	162.0*
Glucose variability SD (mg/dL)	54.2	54.1	54.3	60.7	59.5	72.4
Coefficient of variation CV (%)	36.8	36.5	37.8	40.7	40.2	44.7
Glucose values in different ranges						
<50 mg/dL (%)	0.3	0.1	0.8	0.2	0.2	0.0
<60 mg/dL (%)	0.8	0.6	1.3	0.8	0.8	0.0
<70 mg/dL (%)	3.3	2.8	5.1*	2.8	2.9	1.8
70–180 mg/dL (%)	73.0	73.0	73.2	74.0	74.3	70.0
100–140 mg/dL (%)	33.0	33.9	30.2	33.8	33.5	37.3
>180 mg/dL (%)	23.7	24.2	21.7	23.2	22.8	28.2
>250 mg/dL (%)	5.2	5.3	4.7	7.1	6.6	12.7*
>400 mg/dL (%)	0.1	0.1	0.0	0.3	0.3	0.0

[a] Insulin dosing error.
[b] Insulin dosing errors and workflow deviations.
* Statistically significant difference ($p < 0.05$) * difference ($p < 0.1$).

ations were missed insulin injections leading to elevated BG levels. This is in line with other findings in our study, such as the significantly higher number of values in the hyperglycemic range and larger glycemic variability due to errors. One measure to prevent hyperglycemia could be the implementation of a more intrusive form of reminders. In line with Horsky et al. we doubt the effectiveness of such measures due to alert fatigue and user acceptance problems. Excessive alarming should be reduced and should be performed only in the most dangerous conditions [30]. Compared to Lee et al. GlucoTab® does not introduce blocking interventions but aims to reduce the need for alerts by continuously optimizing insulin doses during ordering and administration [31]. In future versions of GlucoTab® this problem will be addressed by implementing feedback to HCPs about adherence to decision support.

In the PaperG group we observed a markedly lower number of workflow deviations compared to the CompG group due to the possibility to append BG data at a later time. Added data were not detectable and old BG measurements which were used for insulin dose calculation could not be identified due to the lack of precision of documentation times in the PaperG group. The actual frequency of workflow deviations is assumed to be comparable between the groups due to similar workflows. In our setting and probably also in general, paper-based documentation is not suitable to analyze errors of time critical tasks.

No influence of old BG measurements on hypo- or hyperglycemia was observed in the CompG group. Also, the what-if analysis of insulin doses with corrected BG levels from CGM at the time of dose calculation showed no effects. Hypoglycemic events and old BG measurements affecting insulin doses were rare events and the investigations were performed in an already well-structured ward with a small average delay of tasks. In the CompG group the use of measurements which were on average 18.8 min older than the allowed 30 min by the diabetes management system, did not lead to clinically relevant effects. Workflow deviations in the CompG group had a far larger influence on hyperglycemia in T2DM patients than dosing decisions based on old BG measurements.

BG documentation errors identified in this study did not influence the validity of our already published clinical data [23,24]. Compared to recent studies in computerized hospital diabetes management, we found a considerably lower rate of hypoglycemia and at the same time lower or at least equal overall mean BG levels [10,12]. In these previous studies, medication order entry and clinical decision support was directed at physicians only, although diabetes management tasks performed by nurses usually outnumber the tasks performed by physicians. Furthermore, the order set used in these studies did not involve regular follow-up using an algorithm for daily dose adjustment [20,24]. In our study, nurses performed 85% of all tasks (bolus insulin calculations and entering of BG measurements) and 80% of tasks including insulin dose calculations. This led to a majority of errors affecting insulin dose calculations performed by nurses when using paper-based medication management. However, the relative frequency and absolute amount of insulin dosing errors were higher for physicians. In contrast to the current version of GlucoTab® nursing assistants in the CompG group did not have access to directly input BG values into the system which may have contributed to BG transmission errors. It is essential to include all relevant people in medication management of diabetes when using a basal-bolus insulin regimen [32]. Access to therapy relevant information should be available to all HCPs on duty at all times and at multiple locations [33]. Therefore, we are currently working on a web-frontend to allow access from a web browser e.g. in a nurses station, to facilitate an improved integration into hospital workflows.

A poor user interface is the most common cause for technology-related errors [34]. Therefore, the iterative development process for GlucoTab® included usability tests in a clinical environment with diabetes specialists [35]. Paper-based documentation allows deviations from workflow and therefore high flexibility. The implementation of computerized systems supporting clinical workflows is challenging and a large number of special cases have to be considered without compromising usability. GlucoTab® allows manual correction of BG levels and insulin doses and belated entry of values with a time stamp. Impact on the algorithm is automatically handled and appropriate user interaction is initiated if required. In addition, active insulin ('Insulin on Board') is considered to prevent unwanted insulin stacking and in case of delayed administration, long acting insulin doses are reduced. Our analyses did not detect any additional sources of error when using GlucoTab® which showed similar BG control without an increase of hypoglycemic episodes compared to paper-based best practice studies [21,36,37].

Our analysis is limited by non-randomized study groups, but selection bias was minimized because the groups were recruited from all T2DM patients hospitalized at the general ward during a certain period. Patient population did not differ in any relevant parameter. Especially in the CompG group, that had no user calculation errors, the small number of observations limited the analyses regarding the impact of insulin dosing errors on hypoglycemia. The comparison of the overall glycemic control between the two groups may also be influenced by the fact that the distribution of bolus insulin for meals differed in the studies. However, the difference in

Summary table
What was already known on the topic?

- 37% of diabetes patients in a recent diabetes inpatient audit experienced at least one diabetes medication error during hospitalization.
- Medication order entry systems in combination with clinical decision support systems (CDSS) reduce medication prescribing errors, but clear evidence that these systems also reduce adverse drug events is missing.
- Recent guidelines recommend the use of CDSS and medication order entry systems for diabetes therapy in hospitalized patients.

What this study added to our knowledge?

- Manual dose calculations are prone to error and increase the risk of hypoglycemia in diabetic patients. These errors could be entirely excluded by using computerized systems.
- Using medication order entry with decision support including dose calculations reduces the risks considerably, although data transcription of blood glucose measurements still may lead to improper insulin doses.
- In our setting and probably also in general, paper-based documentation is not suitable to analyze errors of time critical tasks.

distribution of bolus insulin did not influence the investigation of frequency of errors and clinical impact of BG documentation- and user-related calculation errors and workflow deviations.

5. Conclusion

We were able to show that the use of a computerized diabetes management system that includes insulin dosing decision support prevents insulin dose calculation errors. Manual insulin dose calculations were the major source of error and had a particularly strong influence on hypoglycemia. A computerized system facilitates the use of more complex insulin dosing algorithms with additional safety features such as 'Insulin on Board' without compromising usability and introducing additional risk for calculation errors. The low number of errors in the CompG group, were predominantly missed insulin injections leading to elevated BG levels. This highlights the importance of a structured approach to hospital diabetes management recommended by clinical guidelines [19]. In our analysis, workflow deviations in the CompG group had a far larger influence on hyperglycemia in T2DM patients than dosing decisions based on old BG measurements.

The performance of diabetes management in both groups was comparable to best practice paper-based clinical studies. Insulin dosing errors and workflow deviations led to measurable changes in clinical outcome. Due to the complexity of inpatient diabetes management, diabetes management systems including decision support should address nurses as well as physicians in a computerized way. Our analysis shows that such systems reduce the frequency of errors and therefore decrease the probability of patients experiencing hypo- and hyperglycemia.

Authors' contribution

KD designed the investigation, performed data processing, statistical analysis and drafted the manuscript. KD and PB interpreted the data. CB provided valuable information for the performed analyses. BH, LS, TP, JM, KN and JP designed the original studies and contributed to a common understanding of the clinical domain, workflow and relevance. TP supervised the original studies and is the grantor of this work. All authors contributed to discussions, critically reviewed the manuscript and approved the final version.

Conflicts of interest

TP is a member in the advisory board of NovoNordisk A/S and received speaker honoraria from NovoNordisk A/S. JM is a member in the advisory board of sanofi and received speaker honoraria from NovoNordisk A/S and Roche Diabetes Care. JP received speaker honoraria from NovoNordisk A/S. The remaining authors declare no duality of interest associated with this manuscript.

Funding

The original studies were partly funded by the European Commission under the 7th Framework Program in the area of Personal Health Systems under Grant Agreement no. 248590 (REACTION project). This work was funded by the Austrian Federal Ministry of Science, Research and Economy—Austrian Research Promotion Agency project number 844737 (Research Studio Austria "GlucoTab")

Ethics approval

The data used for analysis is from studies which were conducted with the approval of the Ethics Committee of the Medical University of Graz.

Clinical trial reg. no. NCT01407289, NCT01932775, http://www.clinicaltrials.gov.

Acknowledgements

The authors thank the nurses and physicians of the Divisions of Endocrinology and Diabetology who supported the original studies and Andrea Berghofer for clinical data monitoring (Endocrinology and Diabetology, Department of Internal Medicine at Medical University of Graz). We thank Selma Mautner and Beate Boulgaropoulos (HEALTH—Institute for Biomedicine and Health Sciences, Joanneum Research GmbH, Graz, Austria) for critical review and editorial assistance with the manuscript. We thank Bernd Tschapeller and Christian Krainer (both HEALTH—Institute for Biomedicine and Health Sciences, Joanneum Research GmbH, Graz, Austria) for clinical data management.

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2. Summary

The post-hoc analysis of a before and after study reported in this chapter was investigating frequency and clinical impact of errors in BG documentation and user-related calculation errors as well as workflow deviations in diabetes management. This analysis is based on two previously published clinical studies and was comparing a paper-based protocol to a computerized medication management system combined with clinical workflow and decision support. Using data from several sources different categories of errors were analyzed in a very detailed way and their effects on medication dosing decisions and clinical relevance were estimated. The outcome of this analysis show that even in a highly standardized environment under study conditions, errors in diabetes management occur. Computerized systems reduce errors, but a potential for errors still remains. The benefit of computerized diabetes management and ways to further reduce error potential were discussed.

Examples for sources of error were falsely remembered or temporarily falsely noted BG values during manual transfer from the POCT device to the medication order entry. Here, the immediate availability and automated handling of BG values from medical devices directly at the point of care has the potential to reduce errors. In contrast to the current version of GlucoTab®, nursing assistants did not have access to directly input BG values into the system which may have contributed to BG transmission errors. It is essential to include all relevant people in medication management of diabetes using a basal-bolus insulin regimen. Access to therapy relevant information should be available to all HCPs on duty, at all times and at multiple locations. Currently, a web-frontend is under development to allow access from a web browser e.g. in a nurses station, to facilitate an improved integration into hospital workflows. Initially during system integration, problems with system performance were due to low Wi-Fi signal strength. The system stayed connected to a Wi-Fi access point with a weak signal even though access points with better signal strength were available. Therefore, a routine was developed which continuously measures signal strength and automatically switches to the strongest signal.

Manual insulin dose calculations were the major source of error in the paper-based group and had a particularly strong influence on hypoglycemia. User calculation errors were entirely excluded by using GlucoTab®. Computerized systems furthermore facilitate the safe use of more complex algorithms with additional safety features, without compromising usability or inducing additional sources of error. In the computerized group, missed or delayed tasks had a significant effect on hyperglycemia, whereas

the use of BG measurements older than 30 minutes for insulin dose calculation was clinically less relevant. Only data provided by GlucoTab® enabled detailed investigations of clinical workflows, and to investigate the clinical impact of workflow deviations. Unfortunately, a lack of precision of documentation times limited analysis of workflow deviations in the paper-based group. In our setting and probably also in general, paper-based documentation is not suitable to analyze errors of time-critical tasks.

Insulin dosing errors and workflow deviations led to measurable changes in clinical outcome. Due to the complexity of inpatient diabetes management, diabetes management systems including decision support should aid nurses as well as physicians in a computerized way. Such systems reduce the frequency of errors and therefore decrease the probability of patients experiencing hypo- and hyperglycemia.

CHAPTER VII

Personalization of the GlucoTab® algorithm - Preliminary considerations

This chapter presents the book chapter "Towards Personalization of Diabetes Therapy Using Computerized Decision Support and Machine Learning: Some Open Problems and Challenges" by **Donsa** et al. 2015 [59].

1. Towards Personalization of Diabetes Therapy Using Computerized Decision Support and Machine Learning: Some Open Problems and Challenges [Donsa et al. 2015]

Towards Personalization of Diabetes Therapy Using Computerized Decision Support and Machine Learning: Some Open Problems and Challenges

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Abstract. Diabetes mellitus (DM) is a growing global disease which highly affects the individual patient and represents a global health burden with financial impact on national health care systems. Type 1 DM can only be treated with insulin, whereas for patients with type 2 DM a wide range of therapeutic options are available. These options include lifestyle changes such as change of diet and an increase of physical activity, but also administration of oral or injectable anti-diabetic drugs. The diabetes therapy, especially with insulin, is complex. Therapy decisions include various medical and life-style related information. Computerized decision support systems (CDSS) aim to improve the treatment process in patient's self-management but also in institutional care. Therefore, the personalization of the patient's diabetes treatment is possible at different levels. It can provide medication support and therapy control, which aid to correctly estimate the personal medication requirements and improves the adherence to therapy goals. It also supports long-term disease management, aiming to develop a personalization of care according to the patient's risk stratification. Personalization of therapy is also facilitated by using new therapy aids like food and activity recognition systems, lifestyle support tools and pattern recognition for insulin therapy optimization. In this work we cover relevant parameters to personalize diabetes therapy, how CDSS can support the therapy process and the role of machine learning in this context. Moreover, we identify open problems and challenges for the personalization of diabetes therapy with focus on decision support systems and machine learning technology.

Keywords: Personalization · Machine learning · Decision support · Diabetes mellitus

A. Holzinger et al. (Eds.): Smart Health, LNCS 8700, pp. 237–260, 2015.
DOI: 10.1007/978-3-319-16226-3_10

1 Introduction

Diabetes mellitus (DM) is a growing global disease which highly affects the individual patient but it also represents a global health burden with financial impact on national health care systems. In 2013 approximately 382 million people were suffering from diabetes. It is estimated that this number will have reached 592 million in 2035. In addition, approximately 175 million diabetes patients are estimated to remain undiagnosed. In the U.S., the total estimated costs for diabetes were $174 billion for the year 2007 [1–3].

DM is a chronic illness of the metabolic system leading to high blood glucose levels. DM can be classified into two main clinical categories. Type 1 diabetes mellitus (T1DM) is caused by the loss of β-cells which are responsible for the storage and release of insulin and it mainly occurs in children, adolescents and young adults. In contrast, type 2 diabetes mellitus (T2DM) is determined by insulin resistance and develops due to a progressive insulin secretory defect, mostly in elderly people with overweight or obesity [4].

In both conditions continuous medical care is required to minimize the risk of acute (e.g. ketoacidosis) and long-term complications (e.g. diabetic foot syndrome, nephropathy, retinopathy, cardiovascular diseases or stroke) [5]. T1DM can only be treated with insulin, whereas a wide range of therapeutic options are available for patients with T2DM [4]. Adhering to therapy in chronic diseases like T2DM requires active participation and is often very burdensome for patients. Furthermore the effects of non-adherence are not immediately evident. Long-term complications like a diabetic foot syndrome or retinopathy take years to develop [6]. Diabetes therapy is complex and therapy decisions comprise various medical and life-style related information.

The availability of smart health technology [7] like continuous glucose monitoring (CGM) [8], physical activity detection [9], location and movement data, image recognition for planned meals [10], data from computerized diabetes diaries offer large data sets which can be used for therapy initialization or the further improvement of the therapy of an individual person suffering from diabetes. The large amount of generated data shows the importance of knowledge discovery in data handling/processing for therapy personalization [11]. Computerized decision support systems (CDSS) aim to improve the treatment process in the hospital [12] as well as at home [13].

In this work we cope with the potential of CDSS in the personalization of diabetes therapy to support the therapy process in different health care sectors and the role of machine learning. Moreover, open problems and challenges for the personalization of the diabetes therapy focusing on CDSS and machine learning technology are identified.

2 Glossary and Key Terms

Clinical Computerized Decision Support systems (CCDSS): 'Clinical Decision Support systems link health observations with health knowledge to influence health choices by clinicians for improved health care' - this definition has been proposed by Robert Hayward of the Centre for Health Evidence.

Computerized Physician Order Entry (CPOE) is a specialized sub-category of hospital electronic patient records for the management of physician orders. Such systems in general can offer reminders or prompts or even go further and perform calculations and offer decision support [14].

Diabetes Mellitus (DM) is a group of metabolic diseases in which high blood sugar levels over a prolonged period occur. DM is classified into two main clinical categories. Type 1 diabetes mellitus (T1DM) results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The source is unknown. In contrast, type 2 diabetes mellitus (T2DM) develops due to a progressive insulin secretory defect in mostly elderly people with overweight or obesity [4, 6].

Diabetes Therapy: The success of a diabetes therapy depends on various factors. Regular measurement of the blood glucose level is the basal requirement for patients suffering from diabetes. The amount of necessary measurements depends on the intensification of the therapy and the progress of the diabetes disease. In contrast to type 1 DM that can only be treated with insulin, a wide range of therapeutic options are available for patients with type 2 DM. These are in the best case lifestyle change with change of diet and increased physical activity, but therapy options also include oral or injectable antidiabetic drugs and insulin administration. Furthermore insulin therapy itself opens a wide variety of different treatment options. The options range from an once-daily injection of a basal insulin dose (least intensive insulin therapy) to basal-bolus-insulin therapy, where a basal insulin dose and several bolus insulin doses are administered every day (intensified insulin therapy).

Glycated Hemoglobin (HbA1c) is a laboratory parameter which serves as a biomarker for the average blood glucose levels in patients over the previous 2 to 3 months prior to the measurement. In specific situations it can also be used as a measure of compliance with diabetes therapy. In diabetes mellitus, higher amounts of glycated hemoglobin have been associated with increased risk for microvascular complications (nephropathy, retinopathy) and to a lesser extend with macrovascular complications [6].

Glycemic Variability (GV) is the fluctuation of the blood glucose values and it is used as an indicator for the quality of diabetes management, as a high GV leads to increased risk of hypo- and hyperglycemic episodes.

Machine Learning (ML) is an algorithm-based and data-driven technique to automatically improve computer programs by learning from experience. Training of machine learning is performed by the estimation of unknown parameters of a model by using training sets. Literature separates between three main ML groups: supervised, unsupervised and reinforced learning.

3 Personalization of Diabetes Therapy

Individualized glycemic management of diabetes patients using insulin or oral antidiabetics is only possible due to recent advances in diabetes therapy, which increased the therapy safety and efficacy. The development of new insulin analogs led to a more predictable behavior of the drugs' blood glucose lowering effect [15, 16]. The first type of oral antidiabetic agents were developed in France in the 1940s [6]. Since then a multitude of new oral antidiabetic agents has been developed using different pharmacological and physiological strategies. Furthermore a paradigm shift happened in diabetes therapy over the past decades which led to patient empowerment and therapy personalization due to improved patient education.

The choice of therapy and potential personalization especially depends on the DM type. T1DM patients exclusively get insulin treatment. They either receive insulin via pump or by multiple daily injections. Here, personalization is possible by fine-tuning the parameters which drive the algorithms for the patient's individual insulin dose calculation [17]. Patients with a high risk of developing T2DM (pre-diabetes) are treated by lifestyle changes (diet change and increase of physical activity). T2DM patients have a broader array of therapeutic choices. Early onset of T2DM is treated by lifestyle changes or oral antidiabetic agents. If an intensification of the diabetes therapy is necessary different strategies involving insulin are treatment options. Here, personalization is possible by setting different treatment goals for the different stages of intensification (stepwise approach) of the insulin therapy [4, 16]. Less intensive insulin therapies comprise fixed insulin doses once a day, either adjusted by the physician at the next routine appointment or by the patient according to a schema. More intensive insulin regimens require multiple insulin doses per day and the consideration of carbohydrate intake and correction insulin for blood glucose levels outside of a target range. Here, personalization is also possible by fine-tuning the parameters which drive the algorithms for the patient's insulin dose. These algorithms are usually less complex than the ones used for T1DM and consequently they allow fewer options for personalization.

Recent guidelines recommend individualized diabetes therapy goals for people with DM [4]. In the current position statement for the management of T2DM the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) placed great emphasis on patient-centered and personalized diabetes care [18]. Personalization of glycemic control targets is based on clinical parameters, including age, duration of DM, prevailing risk of hypoglycemia, presence of DM associated complications or co-morbidities and eco-system components [19]. In specific situations, the patient's glycated hemoglobin (HbA1c) serves as a measure of adherence with diabetes therapy. It is a biomarker for average blood glucose levels over the 2 to 3 months prior to the measurement. In diabetes therapy, certain blood glucose target values and HbA1c targets are defined for the patient's therapy. These targets are also determined by the choice of the patient's therapy option. Insulin for example is very effective in lowering HbA1c but insulin administration also increases the risk of hypoglycemia [16].

Individual therapy goals are set to avoid co-morbidities caused by poor glycemic control. To avoid the deterioration of a retinopathy, a better glucose control which means achievement of lower blood glucose levels and HbA1c targets is recommended [20, 21].

Two other important factors in personalizing diabetes therapy are age and diabetes duration. Consequently, lower targets should be achieved in younger patients to reduce the long-term risk of DM associated complications. In contrast, therapy should aim for safer targets and achieving them more slowly in older patients [22].

The setting in which the therapy is performed also strongly influences the therapy targets. Patients in a nursing home setting have typically less stringent targets to avoid hypoglycemia and less frequent blood glucose monitoring compared to patients in intensive care units [23]. Even though the exact therapy goals for patients in intensive care units are discussed controversially, intensive insulin therapy to maintain blood glucose at lower targets reduces morbidity and mortality in critically ill patients [24, 25].

In this article we focus on personalization of diabetes treatment rather than on all strategies of Personalized Medicine for Diabetes (PMFD), because widespread adoption of this global approach will only occur when the identification of risk factors through genotype or through biomarkers is accompanied by an effective therapy [26]. PMFD uses information about the genetic makeup of a person with diabetes to customize strategies for preventing, detecting, treating and monitoring their diabetes.

The vast amount of parameters for personalization makes diabetes management increasingly complex and diabetes complications remain a great burden to individual patients and the society [27]. Therefore it is hypothesized that the quality of these medical decisions can be enhanced by personalized decision support tools that summarize patient clinical characteristics, treatment preferences and ancillary data at the point of care [28].

4 Towards Personalization Using Decision Support Systems

Diabetes therapy takes place in different health care sectors. Every sector has different goals for the patients' diabetes therapy, as mentioned in the previous chapter. This results in specialized solutions for diabetes management available on the market, each specifically targeting a particular sector. Diabetes decision support systems are used in the following sectors:

1. *Patient self-management*
    a. *At home*
    b. *Primary care*
    c. *Outpatient care*
2. *Institutional care*
    a. *Nursing homes*
    b. *Hospital*
        i. *Inpatient care*
        ii. *Intensive care*

Decision support aiding health care professionals can primarily be found in institutional care, whereas decision support targeting decisions performed by patients can mostly be found in the patient self-management sector. DM patients outside of institutional care settings are on average younger, more independent and the focus of the therapy lies predominately on the diabetes disease. Patients in institutional care are primarily not admitted because of having DM, but for the complications associated with having DM (diabetic foot syndrome, nephropathy, retinopathy, cardiovascular diseases or stroke). DM is mostly regarded as concomitant disease and should therefore cause the least possible additional effort. Strategies for personalization of the diabetes therapy are therefore very different in the health care sectors. The following chapters summarize decision support systems and tools which facilitate a personalization of the diabetes therapy.

4.1 Diabetes Decision Support Applications for Self-Management

Medication support and therapy control: Self-management of the patient's insulin therapy requires the frequent measurement of blood glucose levels and the adjustment of the patient's medication. In *insulin therapy,* the calculation of the required insulin dose involves the use of more or less complicated mathematical formulas. Therefore mathematical aides, integrated into insulin pumps and glucose meters, have been developed which model evidence based protocols for insulin dosage [29], so called *Automated Bolus Calculators (ABC)*. A recent review summarized the current state of the art on 'Glucose meters with built-in automated bolus calculator' [30]. The authors concluded that ABC incorporated in glucose meters can be regarded as bringing real value to insulin treated patients with diabetes. Software apps are not recommended up to now as they generally are of poor quality [31]. ABC allow very detailed personalization of the insulin dosing decision support. Aside from blood glucose levels, ABC also consider carbohydrate intake and physical activity or health events to estimate insulin requirements. 'Automated' bolus calculation means that no manual bolus calculation is necessary. The identification of the correct parameters for personalization of the bolus calculation is a very individual and time consuming process for every user [29].

In the context of insulin-based diabetes therapy, a *controller* is an algorithm that controls the blood glucose values by titrating the amount of insulin. ABC are either rule or model based open-loop diabetes control methods. Independent of the used diabetes control method, it is categorized *open-loop system,* when a patient has the final power of decision [32].

Artificial pancreas systems are used for automated insulin injections. This type of diabetes control is characterized as *closed-loop.* Using these systems, model-predictive control algorithms are applied which use predictions of future glucose levels to estimate insulin requirement in insulin-pump therapy [33]. In these applications the input for the prediction models is continuous glucose monitoring data of T1DM patients.

Models of glucose dynamics for predictive purposes can mainly be divided into two categories; physiologically-oriented models and data-driven methods. The latter approach can furthermore be divided into time series analysis, using auto regressive models and machine learning methodologies [34]. Physiological models for blood

glucose estimations are very accurate for short time predictions. They achieve a predictive capacity with a root mean square error (RMSE) of 3,6 mg/dl for a prediction horizon of 15 min [35]. Main advantages of these models compared to data-driven models are that there is no need to train these models and that their output is physiologically explainable. The main disadvantage is that if the difference is not explainable with the input variables no personalization of the algorithm is possible. *Data-driven glucose prediction* is a relatively new methodology compared to physiological glucose prediction. Similar to the development of the personal computer these technologies advanced in the late 1990s [36]. Main advantages of these models are that they are adaptive (self-learning) and patient specific without the need for developing a physiological model. Main disadvantages are that the system depends on the training data quality (garbage in and garbage out problem) and that the output of the system is not physiologically explainable.

For artificial pancreas systems relatively short prediction horizons and therefore a comprehensive monitoring using CGM are needed to enable closed-loop diabetes control [37]. But also patients without CGM which are not so intensively monitored could benefit from the prediction of future blood glucose levels. In [38–40] the authors devised an engine that predicts the expected blood glucose level at the next meal and the pending risks of hypoglycemia. They performed a study for safety and efficacy of using predicted data in dosing decision support for routine patient care. The prediction engine was used in patients who were referred to begin basal-bolus-insulin therapy. HbA1c levels fell significantly from 9.7 ± 1.7 % (baseline) to 7.9 ± 1.2 % (end of study), and hypoglycemia dropped fourfold.

Decision support tools for physicians: The patient's diabetes therapy is performed in close collaboration with primary care physicians and/or outpatient clinics. In [41] a computer application which helps primary care physicians in diabetes therapy decision making was developed and validated in a cluster-randomized clinical trial. The application was used to make decisions when starting, continuing or changing insulin and its dosage. The HbA1c in the intervention group was significantly reduced by the use of the decision support application (–0.69 %; $p = 0.001$). Electronic decision support tools for primary care physicians are summarizing information about patients' diabetes state, they provide reminders to required diabetes care and a support to patient education [42]. In [66] a CDSS was designed to help outpatient clinicians manage glycaemia in patients with T2DM. A rule-based expert system generates recommendations for changes in therapy and accompanying explanations. As mentioned earlier, T2DM is in contrast to T1DM a disease where a variety of different treatment options exist. Therefore, the system considers 9 classes of medications and 69 regimens with combinations of up to 4 therapeutic agents. The program is integrated in a web-based system for diabetes case management and supports a method for uploading data from glucose meters via telephone network. The system provides a report to the clinician regarding the overall quality of glycemic control and identifies problems, e.g., hyperglycemia, hypoglycemia, glycemic variability, and insufficient data.

Therapy aids and lifestyle support: To aid diabetes patients in the difficult task of estimating the correct personalized insulin requirement and to meaningful perform personalized control of therapy several tools are available.

Carbohydrate estimation: The success of the patient's insulin therapy is significantly dependent on the correct estimation of how nutrition influences insulin requirements [43]. This relationship is used in insulin therapy and it is called the *Carbohydrate Factor*. The factor is patient specific and may vary over the time of the day. Once accurate patient specific factors have been developed for different times of the day, correct estimation of the number of carbohydrates in a meal represents another obstacle in insulin therapy. Many patients might not estimate carbohydrates accurately and commonly either over or underestimate carbohydrates in a given meal [44, 45]. Another source of inaccuracy in estimating the patient's insulin requirement for meals based on carbohydrate counting is the composition of foods. Not only the number of carbohydrates influences the physiological glycemic response but also how the meal is absorbed. For example rich-in-fat meals need more time to be absorbed. Therefore these meals lead to prolonged hyperglycemia or the risk of hypoglycemia, if the insulin dose to cover the expected blood glucose rise for these meals is administered at once [46]. To approach the these problems, bolus calculators with nutrition data base software integrated into an insulin pump have been developed which are able to control the type of bolus [47]. In rich-in-fat meals the bolus is administered using a wave profile to administer insulin over a longer period of time compared to a single bolus.

For easier estimation of the meals' carbohydrate content, it has been proposed to implement nutrition data bases in food recognition systems. These systems use machine learning algorithms to categorize images of food [10, 48]. Therefore it is possible to identify the food by taking a picture of the meal using a smartphone. The systems are now able to detect food with an accuracy of up to 81 %. The final systems for diabetes therapy should include food segmentation such that images with multiple food types can also be addressed. Furthermore, to be eligible for diabetes therapy, the food volume should be estimated using multi-view reconstruction and the carbohydrate content should be calculated based on the computer vision results and nutrition data bases.

Activity recognition: The patient's insulin requirement and therefore the blood glucose levels are strongly influenced by the amount of physical activity and the health status. In diabetes therapy, establishing health benefits from physical activity is primarily done on the basis of self-reported data; typically surveys asking patients to recall what physical activity they performed according to their diabetes treatment plan. This is usually performed in T2DM patients. In T1DM patients using bolus calculators, physical activity often plays a major role in insulin calculation. The extent of change rate of the insulin dose depends on the intensity and duration of physical activity and varies among the patients [49]. Currently, this estimation process is very imprecise due to inaccurate reporting of physical activities. One solution to improve the accuracy of reporting could be automated activity recognition. Such systems consist of [50]:

(1) A sensing module that continuously gathers information about activities using accelerometers, microphones, light sensors, heart rate sensors, etc.
(2) A feature processing and selection module that processes the raw sensor data into features which categorize by activities.
(3) A classification module that uses the features identified in the previous data procession step to infer which activity has been performed.

Methods to predict activity-related energy expenditure have advanced from linear regression to innovative algorithms capable of determining physical activity types and the related metabolic costs. These novel techniques can measure the engagement in specific activity types [51]. Integrated into T2DM therapy, the therapy adherence to physical activity lifestyle interventions could be monitored. In T1DM, these new techniques could help to estimate the possibly required insulin reduction prior to sports using earlier recordings of similar intensive activities.

Activity recognition can also be implemented in a smart home-based health platform for behavior monitoring. In order to recognize activities being performed by smart home residents, machine learning algorithms could be used to classify sensor data streams. The smart home platform could be used to monitor the activity, diet, and exercise adherence of diabetes patients and evaluate the effects of alternative medicine and behavior regimens [52].

Lifestyle support/promotion: In T1DM patients, the loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas results in the body to fail to produce insulin. T2DM is characterized by insulin resistance which, as the disease progresses, may be combined with a relatively reduced insulin secretion [6]. Therefore, the pathogenesis of T2DM, as a not rapidly progressing disease, can be prolonged by lifestyle interventions. Lifestyle intervention options are diets and/or increase of physical activity used to effectively manage patients in the pre-diabetes phase. Nevertheless, lifestyle management remains challenging for both, patients and clinicians. To track lifestyle events a variety of web- or mobile phone-based diabetes diaries are available. Petrella et al. developed a lifestyle support system which facilitates personalized, data-driven recommendations for people living with pre-diabetic and T2DM conditions [53]. The system suggests subtle lifestyle changes to improve overall blood glucose levels. To improve and support therapy adherence, a mobile phone app with lifestyle diary for coaching of the patient based on multiple psychological theories for behavior change has been recently developed. The user automatically receives generated messages with persuasive and personalized content [54]. Such systems can be used to enforce patient's therapy adherence and to help the patient to better understand their diabetes.

Pattern recognition for optimization of insulin therapy: Diabetes therapy leads to an accumulation of data. Sources are glucose data from blood glucose meters or CGM devices, records of diabetes diaries and therapy plans in more or less structured forms and data from different kinds of therapy aids like bolus calculators. The sources of data are often complex and weakly structured resulting in massive amounts of unstructured information. The data interpretation by the physicians and the patients is often performed without or with only weak decision aids. Currently few products enable data analysis using state of the art technologies which could be found for example in predictive analytics.

In a state of the art article targeting emerging applications for intelligent diabetes management, machine learning classification of blood glucose plots was highlighted [55]. The authors cope with the identification of excessive glycemic variability (EGV). The focus of diabetes therapy is to mimic physiological blood glucose profiles as close

as possible. This means to avoid too high and too low blood glucose levels. But, to some extent high and low blood glucose levels are physiologically normal e.g. blood glucose rise after meals. Both upward (postprandial) and downward (interprandial) acute fluctuations of glucose around a mean value activate oxidative stress. As a consequence, it is strongly suggested that a global antidiabetic strategy should be aimed to reduce HbA1c, pre- and post-prandial glucose, as well as glucose variability to a minimum [56]. To the best of our knowledge no guideline-defined metric for classifying glycemic variability exists [57], nor a decision support system which aids in the detection of EGV [58]. Wiley et al. describe an automatic approach to detect EGV from CGM data [59]. Therefore, two physicians independently built a knowledge data base from CGM data which was used for the training of machine learning algorithms for EGV detection. The best performing prediction model achieved an accuracy of 93.8 %. The results of EGV predictions could inform clinical disease management, if a patient used CGM for the week preceding a routine appointment and therefore propose a personalization of the diabetes therapy approach.

Pattern recognition can be used to meaningfully identify blood glucose patterns, highlighting potential opportunities for improving glycemic control in patients who self-adjust their insulin [60]. Skrøvseth et al. conducted a study to identify how self-gathered data can help users to improve their blood glucose management [61]. The participants were equipped with a mobile phone application, recording blood glucose, insulin, dietary information, physical activity and disease symptoms in a minimally intrusive way. Data-driven feedback to the user in form of graphic representation of results from scale-space trends and pattern recognition methods may help patients to gain deeper insight into their disease. Blood glucose pattern analysis can also be found in ABC.

Long-term disease management: During the last decades, research in medicine has given increasing attention to the study of risk factors for diabetes complications. A practical application of risk factor studies is the development of risk assessment models (UKPDS model [62], Framingham model [63]). These models are able to provide a prediction, based on patient characteristics, of the patient's risk to develop diabetes associated complications [64].

In care management, which is facilitated from a payer perspective by health insurance companies, patients receive a personalization of care according to risk stratification. Stratification focuses on whether patients are ill enough to require ongoing support from a care manager. Having less serious chronic conditions warrant more intensive interventions to prevent them from worsening. Fairly healthy patients just need preventive care and education [65].

Risk preventive modelling enables the prognosis of future high-risk and/or high-cost patients, in patients having a chronic disease like T2DM. The models use a combination of factors, such as demographics, clinical parameters, lifestyle factors, family history of diabetes and metabolic traits [66]. Several machine learning techniques have been applied in clinical settings to predict disease progression and have shown higher accuracy for diagnosis than conventional methods [67]. Risk models have been integrated in guidelines and are increasingly advocated as tools to assist risk stratification and guide prevention and treatments decisions in diabetes care [68, 69]. It is hypothesized that with

the prior knowledge of disease risk, the incidence of T2DM could be reduced considerably by implementing preventive measures in high-risk patients [4].

4.2 Diabetes Decision Support Applications for Institutional Care

Systems used in hospitals for management of diabetes care are very generic and they are designed to operate safely for the majority of patients. Currently personalization for patient characteristics plays a secondary role due to two factors: (1) A short length of stay does not allow the empiric development of patient specific factors which are crucial for the personalization of diabetes therapy. (2) Rigid hospital workflows and excessive workload of clinical personnel often prohibits the implementation of individualizations in diabetes therapies. Nonetheless, aside from these restrictions personalization is possible to some extent. Clinical computerized decisions support systems (CCDSS) often model evidence based guidelines which facilitate personalization of the estimation of medication requirements according to laboratory and demographic parameters [70–73].

Medication and workflow support: Clinical physician order entries *(CPOE)* are a specialized sub-category of hospital electronic patient records for the management of physician orders. They can be configured to support glucose management besides many other things. Such systems generally can offer reminders or prompts or go even further and perform calculations and offer decision support [14].

A recent review dealing with CCDSS' impact on healthcare practitioner performance and patient outcomes displayed significant evidence that CCDSS can positively impact healthcare providers' performance with drug ordering and preventive care reminders [74]. Furthermore, a recent diabetes guideline emphasizes the use of CCDSS and CPOE for insulin dosing [75]. This is a particularly important field of decision support because the correct handling of insulin in diabetes patients is prone to error. In a recent audit which investigated the quality of inpatient diabetes care, 36.7 % of the patients experienced at least one diabetes medication error during hospital stay [76]. A current review estimated that an adoption of CPOE systems in hospitals alone without decision support function leads to a 12.5 % reduction in medication errors [77]. A *Cochrane Review* assessed whether computerized advice on drug dosage has beneficial effects on patient outcomes compared with routine care. The review led to the conclusion that computerized advice on drug dosage (oral anticoagulants and insulin) results in a physiological parameter more often in the desired range. Furthermore, it tends to reduce the length of hospital stay compared to the length of hospital stay in routine care. Furthermore comparable or better cost-effectiveness ratios were achieved with computerized advice on drug dosage [78]. Diabetes medication CCDSS in the hospital range from administering and managing oral antidiabetic agents in non-critically ill patients to adjusting insulin infusion in critically ill patients. Insulin infusion in intensive care units is performed according to paper based nurse-directed insulin nomograms that adjust rates of insulin infusion according to the current rate of infusion and the blood glucose reading. These nomograms usually do not take patient-specific blood glucose trends into consideration and patients may oscillate between hypoglycemia and hyperglycemia [79].

By using a computerized insulin infusion algorithm in a CCDSS which also takes into account the patient's sensitivity to insulin, this system was used to safely achieve near normoglycemia in hospital inpatients. Additionally, there was lower incidence of hypoglycemia compared to initial studies [80].

The success that a CCDSS or CPOE is accepted by clinical staff greatly depends on the implementation into existing workflows [81, 82]. Automatic provision of decision support should be performed as part of the clinicians' workflow. Overall, the use of CCDSS and CPOE systems lead to a standardization of processes in clinical workflows.

Recently, a survey to map the current state of implementation of CPOE and CCDSS in Switzerland was performed. According to this survey, the introduction of CPOE in Swiss healthcare facilities is increasing. The types of CCDSS currently in service usually include only basic decision support related to drug, the co-medication or the setting, and only scarcely taking into account patient characteristics [83]. Future decision support tools must be designed to account for both clinical and patient characteristics [28].

5 Decision Support Using Machine Learning Technology

5.1 A Glimpse into Machine Learning Methods for Health Care

Advances in medical signal, image and text acquisition led to an extensive improvement of available patient-related medical data. These amounts of data make it difficult for health care professionals or patients to provide a timely treatment decision [84]. CDSS support the medical decision making process in diagnostics, therapeutics and prognostics in main medical disciplines [74]. Typical CDSS applications can be found for example in radiology, emergency medicine and intensive care, cardiovascular medicine, internal medicine or oncology [85–91].

In CDSS machine learning is an important underlying technology in many applications. For example radiology-based CDSS usually apply pattern recognition techniques based on machine learning for detection of medical conspicuities [92–94]. ECG signal processing used in cardiology is another promising machine learning approach in medical decision support applications [88, 95].

Machine learning is concerned with the question how computer programs automatically improve with experience [96]. Witten et al. [97] proposed *"Things learn when they change their behavior in a way that makes them perform better in future."* Practically, training of machine learning algorithms is performed by estimation of unknown parameters using training sets.

Duda et al. [98] separates between supervised, unsupervised and reinforced learning. In supervised learning (classification) category labels are manually assigned to each pattern by human experts. The set is divided into a training and a test set. The algorithm learns from the training set, which means that discriminating features of the patterns are identified. The test set is used for evaluation of classification quality. High accuracy means, that the features maximize the difference between patterns of different categories and underline the similarity of patterns in the same category. Typical supervised machine learning models are for example Support Vector Machines (SVM), k-Nearest Neighbors (K-NN), Decision Trees, Naïve Bayes, Random Forests and Neural

Networks. Unsupervised learning (clustering) is important if no human expert could or should label patterns. Unsupervised learning models build clusters based on the features of patterns. K-means, hierarchical clustering or expecting-maximization are typical algorithms to solve clustering problems. Reinforced learning follows a feedback mechanism. A feedback is given if a category is correct or incorrect. Based on this feedback, the algorithm should 'take new paths' and consequently improves with experience.

In the following section, typical applications of machine learning in the field of diabetes therapy are presented.

5.2 Application of Machine Learning for Diabetes Therapy

Diabetes therapy depends on medical, demographic and lifestyle-related parameters. These parameters include diabetes type, age, weight, diabetes duration, co-morbidities, blood glucose, physical activity and diet, to name a few examples. Latest innovations in sensor technology (CGM, clothes integrated movement sensors, smartphone-based image recognition) together with improved documentation effort of medical history in electronic patient records, diabetes-related patient diaries or telemonitoring systems provide large and valuable datasets for therapy-related decision making. Machine learning is regarded to be a helpful technology to support diabetes therapy. In the following, selected fields of machine learning in diabetes therapy are described.

Data-driven blood glucose prediction: No information about the physiology of diabetes is necessary in the data-driven blood glucose prediction. This is in contrast to systems which simulate the human physiology of the glucose-insulin regulatory systems. Data-driven techniques mainly rely on collected data and exploit hidden information in the data to predict future blood glucose levels [99].

With the availability and improved accuracy of tight glucose monitoring using CGM devices, research postulated the question if recent and future blood glucose values can be predicted from glucose history [100]. If this would be possible, hypoglycemic events could be detected or short and long term medication could be titrated.

The data-driven prediction of blood glucose can be considered as nonlinear regression problem between medication, food intake, exercise, stress etc. as input parameters and blood glucose value as output parameter [34]. Besides regression models [101, 102] and time series analysis [103], especially machine learning methods like artificial neural networks (ANN) [102, 104–107], support vector machines [108] and Gaussian models [105] have proven to be successful. Daskalaki et al. [109] presented a promising ANN model with a RMSE of only 4.0 mg/dl for a prediction horizon of 45 min for adults with T1DM. 94 % of the predictions were clinically accurate in the hypoglycemic range. Instead of conducting evaluation with real patients in a clinical study already measured data from patients were used for training and evaluation of the models. Thus, real patient data is needed for a final conclusion on the very good performance of the model. Pappada et al. [110] reported a RMSE of 43.9 mg/dl in his study with ten T1DM patients using a neural network model. The model predicted 88.6 % of normal glucose concentrations (>70 and <180 mg/dl), 72.6 % of hyperglycemia (>=180 mg/dl), but only 2.1 % of hypoglycemia (<=70 mg/dl) correctly within

a prediction horizon of 75 min. Data-driven prediction approaches often lack on estimation of hypoglycemic and/or hyperglycemic events due to limited data on low and high blood glucose values [110]. Another problem of blood glucose prediction is the decreasing performance with increasing prediction horizon. Sufficient prediction is only possible in a 5 to 75 min. range [34, 109].

Data-driven prediction methods depend on the frequency and accuracy of available data. CGM measurements are not state-of-the-art in diabetes therapy due to the lack of accuracy and the missing reimbursement by health insurance companies [111].

Hypo-/Hyperglycemia detection: In contrast to the regression problem of blood glucose prediction, the detection of hypo- or hyperglycemic events can be treated as a typical classification problem. For a given set of input parameters, the model should detect if a hypo- or hyperglycemic event will take place. The prediction can be reduced to a binary classification problem which is easier to achieve than a continuous prediction of blood glucose values.

Sudharsan et al. [112] showed that the detection of hypo- and hyperglycemic events for patients with T2DM is achievable with high accuracy, even if only sparse blood glucose values based on self-monitored blood glucose (SMBG) readings once or twice a day are available. They trained the model with data from approximately 10 weeks. The prediction, if a hypoglycemic event will occur within the following 24 hours was achieved with a sensitivity of 92 % and a specificity of 70 %. By including medication information of the past days the specificity was improved to 90 %, although the prediction was narrowed to the hour of hypoglycemia.

Machine learning can also be used to improve the accuracy of CGM systems. Especially in the hypoglycemic range incorrect measurements can occur. Bondia et al. [113] successfully used Gaussian SVM to detect incorrect CGM blood glucose values with a specificity of approximately 93 % and sensitivity with 75 %.

Glycemic variability detection: Glycemic variability (GV), the fluctuation of blood glucose values, is an indicator for the quality of diabetes management due to increased risk of hypo- and hyperglycemic episodes [114]. In order to rate the quality of GV, numerous metrics have been defined in the last decades. Rodbard [58] rated metrics according to their importance and concluded that many metrics are overlapping. He suggested the following five metrics as the most relevant:

(1) SD_T (total variability in data set), (2a) SD_w (the average of the SDs within each day), or (2b) MAGE (average amplitude of upstrokes or downstrokes with magnitude greater than 1 SD), as a measure of within-day variability, and (3a) $SD_{b\ hh:mm}$ (average of all SDs for all times of day), or (3b) MODD (mean difference between glucose values obtained at the same time of day on two consecutive days under standardized conditions) as a measure of between-day variability.

Based on these metrics automated classification tasks can support healthcare professionals to identify patients at risk and to provide therapy suggestions [58]. Detection of GV is usually based on CGM signals which provide a comprehensive dataset of blood glucose values. Machine learning proved to be a valuable method to support the consensus building for a GV metric and to categorize CGM data according to this metric.

Marling et al. [57] applied multilayer perceptrons (MPs) and support vector machines for regressions (SVR) on 250 CGM plots of 24 h on a consensus perceived glycemic variability metric (CPGV) which have been manually classified into four CV classes (low, borderline, high, or extremely high) by twelve physicians. The manual classification was averaged and ten-fold cross validation was used for evaluation. SVR performed better than MPs. This CPGV metric obtained an accuracy of 90.1 %, with a sensitivity of 97.0 % and a specificity of 74.1 % and outperformed other metrics like MAGE or SD.

Controller for insulin-based diabetes therapy: Besides rule-based and model-based control methods, machine learning can be used to control blood glucose values. Machine learning is categorized as model-free method which means that it does not need a mathematical model of the glucose-insulin interaction [32, 115].

Zitar et al. [116] applied two different artificial neural network models; the Levenberg-Marquardt training algorithm of multilayer feed forward neural network (LM-NN) and a polynomial network (PN) as controller for insulin dose titration. Simulations were performed with a data set of 30,000 BG samples from 70 different patients. LM-NN proofed to be superior over PN. The authors stated that LM-NN has the potential to be used as model-free insulin controller.

Lifestyle support: Carbohydrate intake and physical activity are important parameters for the treatment of diabetes. While the former case increases the blood glucose values, the latter is glucose-lowering. Anthimopoulos et al. [10] presented an automated food recognition system using computer vision. They adapted the well-known bag-of-words approach from natural language processing to describe the identified features of the images. The classification was performed with three different supervised classifiers: SVM, ANN and Random Forests (RF). In total 5,000 images of typical European food-sets were available in 11 food classes. 60 % of the images were used for training and the remaining 40 % built the evaluation set. SVM performed best with an overall accuracy of 78 % for the image classification task. Future work will include automated food segmentation and food volume estimation to count carbohydrates. A smartphone-based real-time mobile food recognition system was presented by Kawano et al. [48]. They used bounding boxes to identify food items which have been classified in one of fifty food categories using SVM. Accuracy was 81.55 % taking the top five candidates into account. The automated system also showed better performance than the manual food selection from a hierarchical menu which has been tested in a small user study.

Physical activity detection is an important pre-requisite to estimate the energy expenditure. Ruch et al. [117] used a tri-accelerometer together with parameters like age, gender and weight, to train a decision tree based activity-specific prediction equation (Tree-ASPE) and an artificial neural network for energy expenditure estimation (ANNEE). Tree-ASPE outperformed ANNEE.

Ellis et al. [118] showed that RF classifier can be used to predict physical activity type and energy expenditure using accelerometers. In this study wrist accelerometers were more successful in physical activity detection, while hip accelerometers were superior in energy expenditure estimation.

6 Open Problems

In this chapter we highlight the main challenges for personalization of diabetes therapy. The focus lies on the problems regarding technical implementation rather than on the medical issues of therapy personalization.

Problem 1: Often DM is regarded with secondary importance especially in the clinical domain. This is very understandable because primarily the patients are not hospitalized because of having DM and the clinicians need to focus on the reasons for the admission. The clinicians are often not able to spend much time for the patient's diabetes therapy due to heavy workload and rigid clinical workflows. Therefore one focus in development of CDSS is the optimization of the devices' usability. In a systematic review investigating features critical to the success of CCDSS, the authors discovered that 75 % of interventions succeeded when the decision support was provided to clinicians automatically. None succeeded when clinicians were required to seek out the advice of the decision support system [82].

Problem 2: Modelling the human insulin system is a complex task. Different approaches have been developed in recent decades. The artificial pancreas is still a field of research and no end-consumer system is available on the market. The main reason for this is that precision and usability of continuous blood glucose (CGM) in daily use currently does not meet the needs for such a system.

Problem 3: Diabetes therapy is complex and varies from patient to patient. Success of diabetes therapy depends on many different factors. Nutrition intake, physical activity and current health status influences the specific therapy. Whereas T1DM can only be treated with insulin, for patients with T2DM a wide range of therapeutic options are available. The combination of factors influencing the therapy and the therapeutic options makes personalized therapy initialization and optimization a complex task. In addition, physicians and patients are often reluctant to start insulin donation and to intensify insulin treatment regimens due to the fear of hypoglycemia. Thus, the use of continuous monitoring with on-body sensors (blood glucose, nutrition intake, physical activity, health status) together with intelligent therapy prediction and optimization models can help to initiate and to optimize therapy with reduced risk of safety critical events like hypoglycemia.

Problem 4: Currently there are many freestanding software applications (apps) available for smartphones which calculate bolus doses of insulin. These apps regulate dosing of potentially dangerous insulin, which puts them in the domain of the Food and Drug Administration (FDA). But none have been approved by the FDA. Patients should not use such non-approved medical software because of the risk of being instructed to administer an unsafe dose of insulin [31]. Also in the institutional care sector, systems with decision support functionality are developed in this "grey area". CPOE systems in Europe have not yet been classified as Medical Devices [119]. A discussion is on-going whether vendors classify their products as Medical Devices Class IIa, Class I or not at all. The development process of CDSS is complicated and expensive due to requirements of Medical Device Directive (MDD) conform development.

Problem 5: Especially for the personalization of insulin therapy new sensor technologies integrated in applications like wearable devices are very promising. Using intelligent controllers which are available for example in integrated machine learning approaches [120] in combination with an arrangement of different sensors can lead to a significant improvement of insulin therapy. However, the problematic lies in the accuracy of currently available minimal intrusive sensor systems. Sensors have to be very accurate to prevent errors in insulin dose calculations. Also food and activity recognition systems have to be improved to be eligible for insulin therapy. Closed loop systems, such as artificial pancreas systems face the same problem. Currently, the biggest obstacle for safely running these systems is not the controller algorithm but the accuracy of CGM sensor systems.

Problem 6: Personalization of the patient's diabetes treatment demands patient involvement. The development of factors for personalization requires frequent documentation of relevant events (e.g. blood glucose, meals, physical activity, health status etc.) and adherence to the therapy goals. This human-in-the-loop situation demands special adaptations of CDSS [121]. For elderly, or unexperienced or less motivated patients this may quickly lead to a therapy overload. Unfortunately, the majority of T2DM patients are part of this group. The main challenge is the development of therapy aids which are as least intrusive and interactive as possible.

Problem 7: The treatment of diabetes takes place in different health care sectors (at home, outpatient care, nursing home, hospital care …). Borders between the health care sectors make it difficult to provide a decision support that can be seamless used in every sector. Consequently, the developed CDSS are focused on a special sector and usually interfaces for data-transfer are lacking. These developments make it difficult for patients and for healthcare professionals to initialize and optimize therapy. Future research should focus on cross-border treatment of patients with diabetes.

Problem 8: Machine learning is used to predict blood glucose values. As machine learning is a data-driven method quality of prediction depends on the quality of available data. Very low blood glucose (hypoglycemia) is an adverse event. Consequently, data is sparse which leads to unsatisfactory prediction results for these safety critical situations.

7 Future Outlook

Recent DM guidelines and advances in research and development of diabetes therapy highlight the importance of therapy personalization.

The ultimate goal of technical research in the field of diabetes therapy is to develop an artificial pancreas system. But as long as artificial pancreas systems are still a research field and no commercial product is available, CDSS are valuable tools to assist in the personalized decision making process. On the one hand, machine learning used within the CDSS (e.g. short-term glucose prediction, pattern recognition, physical activity detection) has proven to be a valuable method to support personalized therapy, but on the other hand it has shortcomings in terms of accuracy and usability in the daily routine (e.g. long-term blood glucose predictions, energy expenditure calculation, carbohydrate estimation).

Consequently, future CDSS using machine learning need to improve to be eligible for DM therapy. Personalization of DM therapy using CDSS is a promising future issue and various promising research routes exist.

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2. Summary

Individualized glycemic management of diabetes patients using insulin or oral antidiabetic drugs is only possible due to recent advances in diabetes therapy, which increased the therapy safety and effectiveness. The predictable behavior of the insulin analogs BG lowering effect is probably the most noteworthy achievement. As a result, personalization of the patients' DM therapy is recommended by guidelines and diabetes organizations. There are several patient-specific, but also institutional factors which have to be considered in diabetes therapy. T1DM can only be treated with insulin, whereas for patients with T2DM a wide range of therapeutic options are available. These options include lifestyle changes, such as change of diet and an increase of physical activity, but also administration of oral or injectable antidiabetic drugs. The diabetes therapy, especially with insulin, is complex and therapy decisions include various medical and life-style related information.

Computerized decision support systems aim to improve diabetes therapy in patient´s self-management, but also in institutional care. Every health care sector has different goals for the patients' diabetes therapy and therefore different strategies for personalization. Personalization of the patient´s diabetes treatment is possible at different levels. It can provide medication support and therapy control, which aid to correctly estimate the personal medication requirements and improves the adherence to therapy goals. It also supports long-term disease management, aiming to develop a personalization of care according to the patient´s risk stratification. Personalization of therapy is also facilitated by using new therapy aids like food and activity recognition systems, lifestyle support tools and pattern recognition for insulin therapy optimization.

Latest innovations in sensor technology (CGM, clothes integrated movement sensors, smartphone-based image recognition) together with improved documentation effort of medical history in electronic patient records, diabetes-related patient diaries or tele-monitoring systems provide large and valuable datasets for therapy-related decision making. Considering these large and detailed datasets machine learning is regarded to be a helpful technology, but currently plays only a minor role in diabetes therapy, especially in inpatient diabetes therapy.

There are several challenges associated with the introduction of new technologies for personalization of the diabetes therapy by using computerized decision support and machine learning. New glucose sensors and activity or food recognition systems have to be very accurate to be eligible for insulin dosing decision support. For example, artificial pancreas systems are not limited by the reliability of

predictive control algorithms, but by the accuracy of the currently available CGM systems. Furthermore, because of the special requirements of the users there has to be a strong focus on the usability of such systems. Devices for patient self-management have to be developed for elderly, or unexperienced or less motivated patients to prevent therapy overload. In institutional care, systems have to be developed to perfectly fit into workflows to achieve maximum acceptance by HCPs. As machine learning is a data-driven method, quality of model output depends on the quality of available data. Very low BG levels are adverse events and consequently data is sparse, which leads to unsatisfactory prediction performance in these critical situations. An additional challenge is the development according to the standards of the Medical Device Directive. Many developers try to avoid these regulatory challenges. Especially, many software apps were developed in a "grey area", where it is not certain if they are regulated by the standards of the Medical Device Directive. Given the rapid expansion and broad applicability of mobile apps, the FDA was recently issuing guidance to which the FDA intends to apply its authority. It is only a matter of time until the European Commission catches up with the FDA and closes these regulatory uncertainties.

CHAPTER VIII

Conclusions and Outlook

1. Conclusions and Outlook

Driven by the reported medical benefit of improved inpatient glycemic control, the development of GlucoTab® - a computerized workflow and decision support system - was initiated to support HCPs in diabetes management. This thesis was embedded in the development of GlucoTab® and focused on the evaluation and enhancement of an insulin dosing algorithm for T2DM patients. This chapter summarizes the main findings of this PhD thesis. Detailed technical and methodological discussions can be found in the previous chapters and in the individual publications.

A toolbox to improve algorithms for insulin dosing decision support:

Work for this PhD thesis created a framework/toolbox to evaluate and to "in-silico" test potential modifications of insulin dosing algorithms and to simulate their potential impact on the patients' BG levels. Novel methods for detailed investigations of the performance of the used insulin dosing algorithms were developed. These methods aim to identify ways to make insulin dosing algorithms safer and more effective for all patients. The framework facilitates a standardized integration of data from clinical studies which will facilitate more detailed analysis with larger patient subgroups. The developed framework has successfully been used to derive modifications of a treatment algorithm from clinical data in an effective and reproducible way. The combination of simulation, evaluation and new clinical studies facilitates an improved development process of insulin dosing algorithms. The most promising algorithms can be identified by using simulation before they are being implemented in medical device software and are being tested in expensive clinical studies. For certain modifications of the insulin dosing algorithm a clinical study can be avoided altogether by performing simulations and evaluations with data from previous clinical studies.

Evaluation - Simulation - Improvement:

Evaluations of the patients' glycemic control were performed by using clinical data that describe a diabetes management performance comparable to best practice clinical studies. Therefore, improvements of the insulin dosing algorithm were performed on an already high level. The initial paper-based version of the insulin dosing algorithm already improved diabetes therapy considerably compared to standard care: Average BG levels were significantly reduced and a significantly higher percentage of BG values were in the target range in patients treated with the insulin dosing algorithm compared to standard care [22]. However, detailed investigations of the initial insulin dosing

algorithm using retrospective statistical analysis with additional CGM data and therapy pattern analysis revealed room for improvement, (Chapter III). The potentially safest and most effective versions of modifications of the insulin dosing algorithm were identified by using simulation and patient hazard analysis.

By redistributing the daily bolus insulin a statistically significant reduction of the patients' relatively high noon BG levels and simultaneously reduced afternoon hypoglycemia was achieved. The amount of BG reduction at noon that was predicted by the simulation was confirmed in two clinical studies.

The therapy pattern analysis performed in the work for this PhD thesis detected in some patients a higher need for insulin than initially calculated at the start of the therapy. Moreover, the adjustment of the therapy was not dynamic enough to adjust the TDD to the required amount of insulin during the patients' short hospital stay. Even though the patients received significant amounts of supplemental insulin to correct for high pre-meal BG values, the TDD was not increased. To achieve a more dynamic adjustment of the TDD, different versions for adjustment of the TDD were simulated and the impact of the modifications on the patients' BG level was estimated. The finally selected version demonstrated a more dynamic and safe adjustment of the patients' TDD, (Chapter III, section 2.4).

Taking a closer look by using additional CGM:

One aim of the work for this PhD thesis was to test the capability of CGM to assess the clinical impact and safety of a basal-bolus insulin therapy. Overall a remarkable consistency was found between parameters that evaluate the performance of the basal-bolus therapy based on glycemic information from CGM and capillary BG measurements. Pre-meal and bedtime BG measurements seemed to describe the overall therapy sufficiently, but the amount of the detected hypo- and hyperglycemic episodes differed significantly between CGM and capillary BG measurements. CGM can be used to describe the overall daily routine such as the rise of BG levels after meals and the impact of the applied diabetes therapy [47]. Although there were hurdles in sensor accuracy, CGM provided information that would not have been recognized by solely using capillary BG measurements. Especially during nighttime a substantial additional number of glycemic events below 70 mg/dL was detected using CGM which suggests that a high number of possibly clinically relevant episodes are missed by using only standard BG measurements. Staff shortages and inconvenience for the patients restrict more frequent capillary BG measurements especially at night and CGM could therefore be an attractive alternative or could be used as a supplementary method.

The analyses in this PhD thesis also aimed to identify if the sole use of CGM could be justified for running a basal-bolus insulin algorithm for T2DM patients on a clinical ward. Therefore, methods to evaluate the potential impact of CGM sensor inaccuracies on insulin dose calculation were developed in collaboration with clinical experts, (Chapter IV, section 2). Potential patient hazard was revealed in what-if analyses that recalculated the patients' insulin doses when using glycemic information from CGM. According to these analyses the use of a CGM system with the observed sensor accuracy could lead to potentially life threatening insulin dose calculations and to ineffective treatment.

Even though CGM sensor accuracy is currently limited, the information of glucose trends could still be useful. However, in the recalculations of the patients' insulin doses no information of glucose trends was considered. The combination of BG measurements with high accuracy and CGM systems with high measurement frequency and trend information could be beneficial for hospitalized patients with unstable glycaemia on a basal-bolus insulin regimen. The development of smart insulin dosing algorithms that consider glycemic trend information from CGM could improve insulin dosing and reduce hypo- and hyperglycemia.

Although promising, the sole use of CGM is not recommended for diabetes management by clinical guidelines. The benefit of using CGM is currently limited for the majority of hospitalized T2DM patients, because CGM systems need frequent calibration based on capillary BG measurements and frequent sensor replacement, and additionally CGM is limited by high additional costs and lack of sensor accuracy. But, new technological advances in this field could soon lead to accurate sensors approved for insulin dosing.

Towards personalization of diabetes therapy:

By developing a multiple regression model to predict the patients' mean daily BG value per hospital stay, significant predictor variables were identified that influence the level of glycemic control, (Chapter V). Especially noteworthy predictors are HbA1c, preexisting home insulin therapy, and the type of admission (acute or planned). Subgroup analyses revealed that although mean daily BG was higher for some patient subgroups, the occurrence of BG values below 70 mg/dL was comparable in all subgroups. The insulin dosing algorithm in its current form was safe in all patient subgroups but was not equally effective for all patients [30].

Personalization of the patients' diabetes therapy is recommended by guidelines and diabetes organizations. In a state of the art review relevant parameters to personalize diabetes therapy were

identified, (Chapter VII, [59]). There are several patient-related but also institutional factors which have to be considered in diabetes therapy. Especially therapy of T2DM patients has a wide range of different therapeutic options and their therapy is very individual and influenced by e.g. the patients' insulin resistance, the progression of the chronic disease, prevailing risk of hyperglycemia, co-morbidities, age etc. Additionally, the setting in which the therapy is performed also strongly influences therapy targets. Patients in a nursing home or at home have less stringent therapy targets than patients admitted to an ICU.

Therefore, computerized decision support systems aim to improve the treatment process in patient's self-management but also in institutional care. Latest innovations in sensor technology (clothes integrated movement sensors, smartphone-based image recognition) together with improved documentation effort of medical history in electronic patient records, diabetes-related patient diaries or tele-monitoring systems provide large and valuable datasets for therapy-related decision making. Considering these large and detailed datasets, machine learning is regarded to be a helpful technology, but currently plays only a minor role in diabetes therapy. Machine learning could be helpful for diabetes therapy that applies methods requiring predictive analytics. The identification of relevant patient-specific parameters influencing therapy and the optimization of the patients' therapy by pattern recognition could also be fields of application using our pooled data source.

Clinical benefit of computerized workflow and decision support:

The clinical benefit of computerized systems for medication order entry and clinical decision support is controversially discussed [60], [61]. There is clear evidence that systems for medication order entry and clinical decision support reduce medication errors, but clear evidence that the combination of these systems reduce clinical adverse drug events is still missing [16]. However, recently published guidelines and studies recommend the use of CDSS and medication order entry systems for diabetes therapy in hospitalized patients [8], [13]–[15].

One aim of the work performed in this PhD thesis was to investigate the frequency and clinical impact of errors in BG documentation and manual insulin dose calculation as well as workflow deviations in diabetes management. In the course of the GlucoTab® development, diabetes management was first tested in a paper-based way and was then implemented into GlucoTab® [22], [30]. Medication errors in the two previously published studies were compared in a post-hoc analysis of a before and after study, (Chapter VI). By using data from several sources, different categories of errors were analyzed in a very

detailed way and their effects on medication dosing decisions and clinical relevance were estimated. The outcome of this analysis show that even in a highly standardized environment under study conditions, errors in diabetes management occur. Computerized systems reduce errors, but a potential for errors still remains. The benefit of computerized diabetes management and ways to further reduce error potential were discussed.

Insulin dosing errors and workflow deviations led to measurable changes in clinical outcome in this study. The analyses show that manual dose calculations are prone to error and increase the risk of hypoglycemia in diabetic patients. These errors could be entirely excluded by using computerized systems. The use of medication order entry with decision support including dose calculations reduces the risks in diabetes management considerably, although data transcription of BG measurements still may lead to improper insulin doses. Therefore the immediate availability and automated handling of BG values from medical devices directly at the point of care has the potential to reduce errors. Implementing a computerized system into the complex workflow of a hospital is challenging and a large number of special cases have to be considered without compromising usability. But if the implementation is performed thoroughly, computerized systems facilitate the use of more advanced insulin dosing algorithms without inducing potential user-errors. An example for a safety feature of an insulin dosing algorithm which requires computerized handling is "insulin on board" in GlucoTab®, which frequently led to insulin dose reductions even under study conditions, (Chapter III, section 2.3). Additionally, the need for computerized assistance in diabetes management is evident in the high number of user-related calculation errors performed by HCPs using paper-based insulin dosing algorithms, (Chapter VI).

Outlook - Improvement in diabetes therapy:

The desired predicted behavior of the simulated modifications of the insulin dosing algorithm was confirmed in clinical studies. Even with these promising results there still remains room for improvement especially at an individualized level. The preliminary investigations of the used rules for calculating the patients' starting TDD, based on age and serum creatinine level, demonstrated that they have to be questioned and that more relevant patient-specific parameters have to be derived. Future versions of the insulin dosing algorithm should improve this dose-finding process at the start of the patient's diabetes therapy to enable a safer and more effective therapy start.

Additionally, the detailed evaluation of safety and effectiveness of the insulin dosing algorithm revealed that even with the refined algorithm in some patients the glycemic targets were not accomplished. One reason for too much or too little insulin in some patients could be the generic insulin scheme. In patients with a small TDD the rigid scheme results in proportionally larger supplemental insulin doses than in patients with a high TDD. Furthermore, only few HCPs modified the insulin sensitivity parameters during the patients' diabetes therapy. That may be reasons for insufficiently controlled hyperglycemia, but may also be reasons for too much insulin resulting in hypoglycemia. On average patients with high BG levels needed more supplemental insulin than currently is provided, but in a few patients this could lead to hypoglycemia. Unfortunately we are currently not able to classify these patients in advance. In a first step, assisted selection of the patients' parameters for insulin sensitivity may be a way to achieve safer and better control by using the current supplemental bolus insulin scheme. In a subsequent step, individualization of the supplemental bolus insulin scheme, e.g. by using corrective bolus insulin in relation to the patients' TDD could also potentially increase safety and effectiveness of the therapy.

The GlucoTab® approach in its current version requires the injection of long-acting insulin around noon and the insulin dosing algorithm is adjusted to this. However, it is foreseeable that on some wards, the administration of long-acting insulin will be favored in the evening or in the morning. Additionally, there are also medical reasons for the injection of the long-acting insulin at other daytimes than noon. The requirement of insulin to control high BG levels is highest in the morning-noon interval. This is physiologically normal in patients, but is also partly attributable to a fading basal insulin action in the morning because of the administration of long-acting insulin at noon [46]. To compensate this fading basal insulin action the bolus insulin dose in the morning was increased. Here, the administration of long-acting insulin at other daytimes than noon would prevent a fading basal insulin action in the morning and could help to control high BG levels in the morning-noon interval. However, by preventing fading basal insulin action in the morning by changing the time of long-acting insulin administration, in some patients the increased bolus insulin dose in the morning could result in hypoglycemia around noon. Before testing this feature in a clinical study, "in-silico" simulation and evaluation of the impact of this modification should be performed and again fine-tuning of the daily bolus insulin distribution should be considered.

The consideration of relevant patient-related and institutional factors in the insulin dosing algorithm could furthermore improve the therapy in patient subgroups. Hypoglycemia did not occur clustered in

patient subgroups, but a significant relationship with the patients' average daily BG and factors such as HbA1c, preexisting insulin home therapy or type of admission was observed. In future versions of the insulin dosing algorithm fine-tuning of algorithm parameters according to the impact of these predictive factors could improve the therapy.

The ADA recently released a new guideline for diabetes care in hospitals [62]. Compared to the more stringent target range of 100 – 140 mg/dL recommended in previous years, a target range of 140 – 180 mg/dL is currently recommended for non-critically ill patients treated with insulin. However, this recommendation is only based on supportive evidence from poorly controlled or uncontrolled studies or on conflicting evidence with the weight of evidence supporting the recommendation. The current version of the GlucoTab® system aims for therapy targets of 100 – 140 mg/dL, but customizable therapy targets are already planned to achieve them safely in all patients.

The successful implementation of computerized decision support systems in clinical wards is often impaired by acceptance problems of HCPs with new devices or new procedures. Especially in diabetes management which requires complex and interdisciplinary cooperation of HCPs, a strong focus during the development of decision support systems should be placed on usability and workflow integration. A better integration of the GlucoTab® system into hospital workflows, facilitated through better accessibility of the system by using a web-frontend, and the automated availability of BG measurements from POCT devices, has the potential to reduce errors. Additionally, the support of other therapy regimens, such as basal-only and basal plus, is under development. In combination, with the already planned algorithm-supported therapy regimen for pre-mixed insulin, features like discharge management, and the integration into the hospital electronic medical record, this should maximize the acceptance of the GlucoTab® system on clinical wards.

The insulin dosing algorithm used by GlucoTab® proofed to be very adjustable, and additional modifications are already planned. In the future it may be necessary to modify the insulin dosing algorithm to support: long-acting insulin analogues with a duration of action longer than 24 hours, the combination of insulin with GLP-1 analogues, insulin pumps in the hospital, or insulin dosing with additional BG trend information from CGM. Additionally, the discovery of new biomarkers which predict for example the patients' insulin sensitivity could lead to modifications of the insulin dosing algorithm. Linear regression models to identify relevant predictor variables for diabetes therapy were limited by potential nonlinear or random dependencies in our data source. Future versions of the

GlucoTab® insulin dosing algorithm could be improved by the use of more complex regression models which are found for example in mixed-effects models or machine learning.

The combination of the evaluation and simulation process with the very adjustable insulin dosing algorithm provides a good preparation for necessary future modifications. Algorithm based computerized decision support systems directly influence clinical practice and have the potential to achieve significant and clinically relevant improvements.

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Acknowledgements

This thesis is based on my work carried out from 10/2012 to 03/2016 at JOANNEUM RESEARCH Forschungsgesellschaft mbH at the Institute for Biomedicine and Health Sciences and was partly funded by grants from the European Commission: EC-Project REACTION (http://reaction-project.eu FP7 248590) and the Austrian Federal Ministry of Science, Research and Economy – Austrian Research Promotion Agency project number 844737 (Research Studio Austria "GlucoTab").

I express my particular appreciation to Peter Beck, Lukas Schaupp and Christian Baumgartner for their invaluable assistance in medical, technical, methodological, scientific and editorial matters. Thanks for supervising and mentoring me!

In addition I thank those who actively or passively contributed to this work:

- my colleagues at JOANNEUM RESEARCH: Reinhard Moser, Thomas Truskaller, Bernhard Höll, Stephan Spat, Christian Krainer, Bernd Tschapeller, Beate Boulgaropoulos and Selma Mautner
- the CRC staff and the medical staff of MUG: Katharina Neubauer, Johannes Plank and Julia Mader
- all the physicians and nurses in the clinical studies
- all the patients that participated in the clinical studies

Special thanks go to my parents Edith and Peter, to my brother Mario and to my girlfriend Madlen who supported me in these stressful, wonderful and educational times!

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Author's publications

In the following the author's peer-reviewed publications, patent applications and conference contributions are listed. My peer-reviewed published first authorship which has not been reprinted throughout the chapters of this PhD thesis is reprinted thereafter.

JOURNALS

K. Donsa, P. Beck, J. Plank, L. Schaupp, J. K. Mader, T. Truskaller, B. Tschapeller, B. Höll, S. Spat, and T. R. Pieber, "A toolbox to improve algorithms for insulin-dosing decision support.", *Applied Clinical Informatics*, vol. 5, no. 2, pp. 548–56, 2014.

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K. M. Neubauer, J. K. Mader, B. Höll, F. Aberer, **K. Donsa**, T. Augustin, L. Schaupp, S. Spat, P. Beck, F. M. Fruhwald, C. Schnedl, A. R. Rosenkranz, D. B. Lumenta, L.-P. Kamolz, J. Plank, and T. R. Pieber, "Standardized Glycemic Management with a Computerized Workflow and Decision Support System for Hospitalized Patients with Type 2 Diabetes on Different Wards.", *Diabetes Technology and Therapeutics*, vol. 17, no. 10, pp. 685–92, 2015.

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BOOK CHAPTERS

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PATENT APPLICATIONS

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CONFERENCE CONTRIBUTIONS (oral communications, posters)

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K. M. Neubauer, F. Aberer, J.M. Mader, B. Höll, L. Schaupp, S. Spat, P. Beck, **K. Donsa**, J. Plank, T. R. Pieber, Safety and efficacy of standardised glycemic management by using the GlucoTab system for patients with diabetes mellitus type 2 at different hospital wards. in 8th International Conference on Advanced Technologies and Treatments for Diabetes (attd), 2015; vol. 17: A26-A26. [Oral Communication]

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J. K. Mader, K. M. Neubauer, L. Schaupp, F. Aberer, **K. Donsa**, T. Augustin, B. Höll, S. Spat, P. Beck, J. Plank, T.R. Pieber, Vergleich von zwei Algorithmen zur Basis-Bolus-Insulintherapie bei Patienten mit Diabetes mellitus

Typ 2 im Krankenhaus. Diabetologie und Stoffwechsel. 2014; 9(Supp.1):S8-S9.-Diabetes Kongress 2014 - 49. Jahrestagung der Deutschen Diabetes Gesellschaft (DDG); MAY 28-31, 2014; Berlin, GERMANY. [Oral Communication]

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Research Article – ehealth2014 special topic aci Applied Clinical Informatics 548

A toolbox to improve algorithms for insulin-dosing decision support

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Keywords
clinical decision support systems, workflow; algorithms; computer simulation; diabetes mellitus type 2

Summary

Background: Standardized insulin order sets for subcutaneous basal-bolus insulin therapy are recommended by clinical guidelines for the inpatient management of diabetes. The algorithm based GlucoTab system electronically assists health care personnel by supporting clinical workflow and providing insulin-dose suggestions.
Objective: To develop a toolbox for improving clinical decision-support algorithms.
Methods: The toolbox has three main components. 1) Data preparation: Data from several heterogeneous sources is extracted, cleaned and stored in a uniform data format. 2) Simulation: The effects of algorithm modifications are estimated by simulating treatment workflows based on real data from clinical trials. 3) Analysis: Algorithm performance is measured, analyzed and simulated by using data from three clinical trials with a total of 166 patients.
Results: Use of the toolbox led to algorithm improvements as well as the detection of potential individualized subgroup-specific algorithms.
Conclusion: These results are a first step towards individualized algorithm modifications for specific patient subgroups.

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Appl Clin Inform 2014; 5 548–556
http://dx.doi.org/10.4338/ACI-2014-04-RA-0033
received: April 3, 2014
accepted: April 30, 2014
published: June 11, 2014
Citation: Donsa K, Beck P, Plank J, Schaupp L, Mader JK, Truskaller T, Tschapeller B, Höll B, Spat S, Pieber TR. A toolbox to improve algorithms for insulin-dosing decision support. Appl Clin Inf 2014; 5: 548–556
http://dx.doi.org/10.4338/ACI-04-RA-0033

1. Introduction

Poor glycemic control has been associated with poor clinical outcome and increased mortality in patients with and without history of diabetes [1]. Recently performed audits in Great Britain demonstrated that glycemic control is not established satisfactorily. Nearly 40% of patients included in the audit experienced at least one diabetes medication error while in hospital. Patients with medication errors were more than twice as likely to experience a severe hypoglycemic episode (16.8%) than patients who did not have a medication error (7.5%) [2]. Implementing a standardized subcutaneous insulin order set promoting the use of scheduled basal and nutritional insulin therapy is a key intervention in the inpatient management of diabetes. Observational and randomized controlled studies indicate that when glycemic control improves, hospital complication rates are lowered in general medical and surgery patients [3–7].

GlucoTab, an algorithm based workflow and decision support system for non-critically ill patients with diabetes mellitus type 2, was developed in the EU-funded project REACTION. It is a mobile Android-based tablet PC which interacts with a Java Enterprise server to provide workflow and insulin dosing support to physicians and nurses directly at the point of care. The GlucoTab system was developed by an interdisciplinary team of engineers, physicians and nurses. Design input was provided by clinical specialists and technical experts, and the system was improved in an iterative approach involving end user feedback.

Four clinical trials regarding patient safety, efficacy of glycemic control and usability have already been performed using the GlucoTab system. The first trial evaluated the underlying workflow-integrated algorithm for basal-bolus insulin therapy in a paper-based form. The algorithm was effective in establishing glycemic control, and was well accepted by medical staff [8]. Subsequently, this algorithm was integrated into the GlucoTab system and applied and evaluated in clinical trials. Although the overall glycemic control was good (73% of blood glucose readings in the accepted glycemic range 70–180 mg/dl), some patient subgroups did not reach the glycemic target range or experienced hypoglycemic episodes.

We now report on a new toolbox for analyzing and simulating GlucoTab system modifications. The ultimate aims of this toolbox development were: to improve the GlucoTab algorithm which in its initial form lacked flexibility, to test and optimize new ideas and hypotheses for algorithm modifications to draw maximum benefit from future clinical studies, and to identify individualized algorithm and workflow improvements for specific patient subgroups. We have now incorporated several heterogeneous clinical data sources and implemented a standard procedure for statistical analysis.

2. Methods

This section summarizes the methods and technologies and the iterative process used to develop the toolbox for improving the algorithms for insulin-dosing-decision support. The toolbox consists of three main components (▶Figure 1):

- **Data preparation:** Data from several heterogeneous sources is extracted, cleaned and stored in a uniform data format.
- **Simulation:** Modified versions of the algorithm are applied in simulations of the treatment workflow, based on real data from clinical trials.
- **Analysis:** The algorithm performance is measured and visualized for all patients or patient subgroups.

2.1 Data preparation

The purpose of this component is to extract, transform and load (ETL) data from clinical trials and other sources into a uniform data structure in a standardized process. One major challenge in the performance of pooled data analyses is the varying structure of data from different clinical trials. We designed a multi-step process to monitor and clean the data: the first steps are performed routinely as part of clinical trial data management according to Good Clinical Practice (GCP) and Inter-

national Conference on Harmonisation (ICH) [9]. In each clinical trial data is extracted from the sources and transformed into a standardized format according to standard data management: data is first checked for consistency and quality; applying for example summary statistics and row checks in the form of if clauses. Inconsistent, implausible or missing values are discussed with the clinical trial team in the database release meeting to achieve a clean dataset for statistical analysis. As part of the toolbox, during the data preparation step, the data is extracted, cleaned and stored in a uniform data format for pooled statistical analyses. Type and unit conversions as well as preparations for the simulations and analyses are performed in this step. Patient-specific profiles with baseline characteristics, concomitant diagnoses and medications, overall glycemic information (mean blood glucose levels, glucose variability, hypo- and hyperglycemic events) and information on the algorithm version used are generated. "Virtual insulin sensitivity" profiles are also generated which are required for blood glucose estimations, performed in the simulation component (see chapter 2.2 Simulation).

2.2 Simulation

Simulation aims to estimate the effect of insulin dose changes on blood glucose values due to algorithm modifications. Simulations are performed with a simulator application implemented in Java which integrates and uses original components from the GlucoTab server implementation. This approach was chosen because building on the original, well tested medical device software components is much more reliable and resource-effective compared to completely rebuilding the entire workflow and decision support algorithm in its full complexity in statistics software and keeping it in synchronization with future modifications of the server. Furthermore, the source code developed for the simulation is already available for implementation into the GlucoTab system, in case of adopting algorithm modifications after the simulation. After additional reviews and testing, the code can be included in the medical device software.

Simulations are performed in two steps, with real patient data from the GlucoTab clinical trials. In the first step, the simulator uses blood glucose measurements and insulin dose calculations, as well as therapy adaptations, based on the original entries into the GlucoTab system by the clinical personnel. Sequentially new insulin dose calculations are performed by using the new algorithm. In a second step the blood glucose estimations are performed. We identified several methods for blood glucose estimations from a structured literature research. Neural networks have been shown to be the most promising technologies [10, 11]. However, neural networks could not be used to achieve accurate blood glucose estimations using our data. The GlucoTab approach for type 2 diabetes mellitus does not involve exact carbohydrate counting. Therefore, exact amounts of carbohydrates consumed were not available and could account for the inaccurate estimations achieved with neural networks. Thus we developed a new method for blood glucose estimations in the toolbox by using "virtual insulin sensitivity" profiles. "Virtual insulin sensitivity" was defined as the difference between two blood glucose measurements divided by the injected insulin dose. A „virtual insulin sensitivity" value is estimated for every measurement interval (e.g. noon to evening) for every patient on each hospital day. The simulator uses the "virtual insulin sensitivity" profile of the patients and calculates the estimated blood glucose value for the next interval alongside the new insulin dose. An example of how blood glucose estimations due to algorithm modifications are performed is illustrated in ▶Figure 2. A patient with a noon blood glucose level of 200 mg/dl, an evening blood glucose level of 160 mg/dl received 10 insulin units (IU) injected at noon, and thus has a "virtual insulin sensitivity" of 4 mg/dl/IU. In this example, one unit of insulin lowers the blood glucose level by 4 mg/dl. In the simulation the patient receives 15 IU at noon, following the dose suggestion of the modified algorithm. Considering the "virtual insulin sensitivity" of the patient the simulation estimates that the additional 5 IU would have lowered the blood glucose level by additional 20 mg/dl resulting in an evening blood glucose level of 140 mg/dl.

All records resulting from the simulations are stored in the relational GlucoTab database, and are then extracted by the data preparation component and prepared for pooled statistical analysis in the analysis component.

2.3 Analysis

In the analysis component, different methods of the toolbox (e.g. patient hazard analysis, what-if analysis) are combined depending on the specific research question. Results from the analysis component are summarized in a reporting tool. The following use cases demonstrate the possibilities of the toolbox by using data from three clinical trials and comprise datasets from the following data sources:

- **GlucoTab server:** 5,218 blood glucose measurements (Roche Accu-Chek) from 166 patients on 1,124 patient days, suggested and confirmed bolus and basal insulin doses and information on consumption of meals and insulin sensitivity
- **Clinical trial data management system (OpenClinica):** Diagnoses, medications and baseline characteristics of 166 patients
- **Laboratory information system:** Hospital laboratory data of 99 patients
- **Continuous Glucose Monitoring (CGM):** 14,140 hours recorded with CGM (Medtronics iPro2) of 97 patients

Pooled data

The first use case demonstrates methods for the retrospective analysis of pooled patient data. It aims to detect the quality of glycemic control when using the GlucoTab system by identifying individualized versions of insulin-dosing algorithms for specific patient subgroups. A penalty scoring system evaluates the therapy of each patient considering the average blood glucose levels, hypo- and hyperglycemic events and glucose variability. If the patient's glycemia is within the target range the scoring system rewards credit points whereas blood glucose values outside the target range are given penalty points. Penalty points are weighted according to the severity of hypo- or hyperglycemia. Hypoglycemia has a higher impact on the score. Subgroup analyses using hierarchical clustering allow the detection of "responder" or "non-responder" patient subgroups and their distinctive properties.

Algorithm modification

The second use case aims to evaluate algorithm modifications. In what-if analyses, outcomes regarding blood glucose levels and suggested insulin doses are investigated and visualized for interpretation by clinical specialists. Patient hazard analyses for patients with low glycemic events are performed to identify the safest version of the modified algorithm: insulin dose calculations are simulated by using new variants of the algorithm. To detect potentially dangerous changes in the algorithm, a potential increase of insulin doses prior to a low glycemic event is investigated. Patient hazard analyses are discussed with diabetes specialists to ensure that only safe variants of a new algorithm are implemented.

Continuous glucose-monitoring data

The third use case considers additional input from continuous glucose monitoring (CGM) data for algorithm evaluation. The clinical standard for monitoring the patient's blood glucose levels is point of care testing (POCT) [12]. POCT provides only a snapshot of the patient's glycemic profile. With the use of CGM we investigated if these snapshots are sufficient for the patient's therapy. We identified low glycemic episodes using CGM data. A low glycemic episode was defined as a signal drop below the threshold level of 70 mg/dl for at least three consecutive measurements (5 min sampling). If the sensor level was above the threshold for less than one hour between two below-threshold episodes, this was counted as one episode. Additionally, to compensate data processing of the CGM sensor manufacturer, offset correction was applied to the CGM sensor data to increase the sensitivity for detection of low glycemic events in a post-processing step. The sensitivity is defined as the relative number of true low glycemic episodes that have been detected. It is calculated as the proportion of the number of detected true low glycemic episodes divided by the number of detected and missed low glycemic episodes [13]. Another aim is to relate CGM to the algorithm: in a subsequent what-if analysis the patient's outcome is investigated regarding suggested insulin doses and patient hazard.

The **reporting tool** generates automated PDF reports using the R project for Statistical Computing [14] with Sweave and LaTeX. A multitude of customized graphic output functions has been de-

veloped using ggplot and ggplot2 packages. Results can be reported as text, tables or figures by using the customizable PDF reports (e.g. ▶Figure 3 and ▶Figure 4 in this paper).

3. Results

Pooled data

Since low glycemic events are the most dangerous in blood glucose management, first analyses were conducted to investigate and visualize the glycemic range which is most likely resulting in low blood glucose events. ▶Figure 3 shows data from all patients treated with the first version of the algorithm (n = 52), revealing that low glycemic events do not only emerge from patients with low blood glucose levels but also occur in patients with initially high blood glucose values.

Algorithm modification

An example of validating the simulation results of the toolbox is demonstrated in ▶Figure 4. The use of the first version of the algorithm in previous clinical trials has resulted in relatively high mean blood glucose values at noon [8] (▶Figure 4a). A blood glucose estimation was performed to simulate a change of the bolus ratio for morning, noon and evening, for all 52 patients treated with the first version of the algorithm (▶Figure 4b). The new algorithm (v2) was clinically validated after implementing the proposed bolus ratio changes into the GlucoTab system. The results for the first 15 patients (▶Figure 4c) showed a significantly reduced mean noon blood glucose level (t-test, p = 0.014).

Continuous glucose-monitoring data

The toolbox was used to assess if POCT provides all necessary information for the patient's glycemic control, especially low glycemic events. Low glycemic events were identified according to the method described (see CGM in the methods section) using 1,480 paired blood glucose sensor readings (8,578 hours recorded with CGM) of 59 patients. After adjusting for the offset of sensor data, 134 events below 70 mg/dl were detected with CGM compared to 35 detected by blood glucose POCT. The majority of low glycemic events that were detected with CGM occurred during the night. Sensitivity to detect low glycemic events using CGM was 42%.

4. Discussion

This work created a toolbox with three main components to improve an insulin dosing algorithm used in a decision support system. The data preparation component enabled a fast and standardized way to incorporate additional clinical data for the simulation component and the analysis component. Based on the uniform data structure and standardized processes, algorithm changes were simulated, evaluated and optimized before being implemented in the decision support system. Three particularly important examples for the use of the analysis component during algorithm development are demonstrated in this paper.

The toolbox was used for pooled data analyses and indicated that low glycemic events occur not only in patients with low blood glucose levels but also in patients with initially high blood glucose levels. A further increase of insulin doses would lead to an increased hypoglycemia risk in some patients. Pooled data analyses and visualization of results were successfully used to investigate a hypothesis and discuss results with clinical experts for a further improvement of the algorithm.

Simulated bolus ratio changes and blood glucose estimations in the toolbox were confirmed with real patient data after the algorithm changes had been implemented in the GlucoTab system. Algorithm changes resulted in a statistically significant reduction of blood glucose levels at noon as estimated by the toolbox, but might have also been affected by the difference in glycemic control prior to the trial. HbA1c in patients treated with the initial version of the algorithm was 76±30 mmol/mol

compared to 62±18 mmol/mol in the first 15 patients treated with the modified version of the algorithm. Further analyses with a bigger sample size are still ongoing.

CGM data indicate that a high number of low glycemic events (<70 mg/dl) are not detected with standard glucose POCT, in particular during the night when fewer POCT reference measurements are available for confirmation. The high number of low glycemic events has to be interpreted cautiously due to the low sensitivity of the commercially available CGM sensor. The sensitivity of the CGM sensor system applied in the studies to detect low glycemic events (42%) is comparable to a recently published study using a similar CGM system (CGM-sensor sensitivity: 37.5%) [13].

The presented toolbox provides the technical foundation for the development of more individualized algorithms. Already planned clinical trials using the GlucoTab system will provide more data for the toolbox and enable us to perform simulations of algorithm changes for various patient subgroups. We will continue in-depth analyses and carefully test algorithm modifications by simulations, before any changes are implemented in the software, and are applied in the therapy of patients in clinical evaluation trials.

Clinical Relevance

Algorithm based decision support systems directly influence clinical practice and have the potential to achieve significant and clinically relevant improvements. The developed toolbox has successfully been used to derive modifications of a treatment algorithm from clinical data in an effective and reproducible way. The safest and best performing algorithms can be identified by simulation, before being implemented in medical device software and being applied in the therapy of patients.

Conflict of Interest

The authors declare that they have no conflicts of interest in the research.

Human Subjects Protections

The procedures used have been reviewed in compliance with ethical standards of the responsible committee on human experimentation.

Acknowledgments

Development of the GlucoTab system and clinical trials were performed within the project REACTION, funded by the European Commission (FP7–248590).

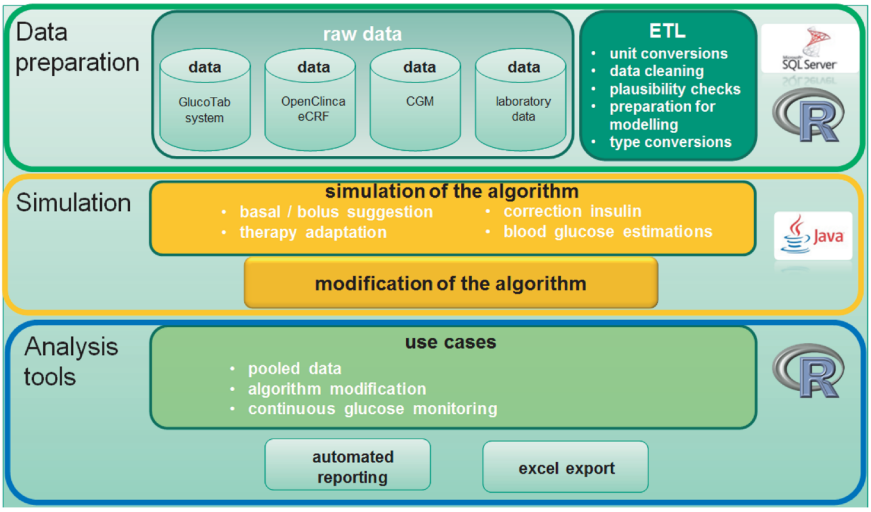

Fig. 1 Structure of the toolbox for improving algorithms for insulin-dosing-decision support. ETL (extract, transform and load)

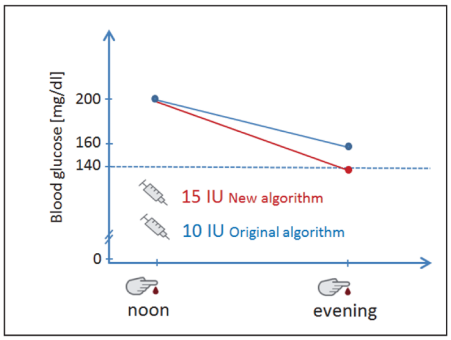

Fig. 2 Example of blood glucose estimations due to algorithm modifications. IU (insulin unit)

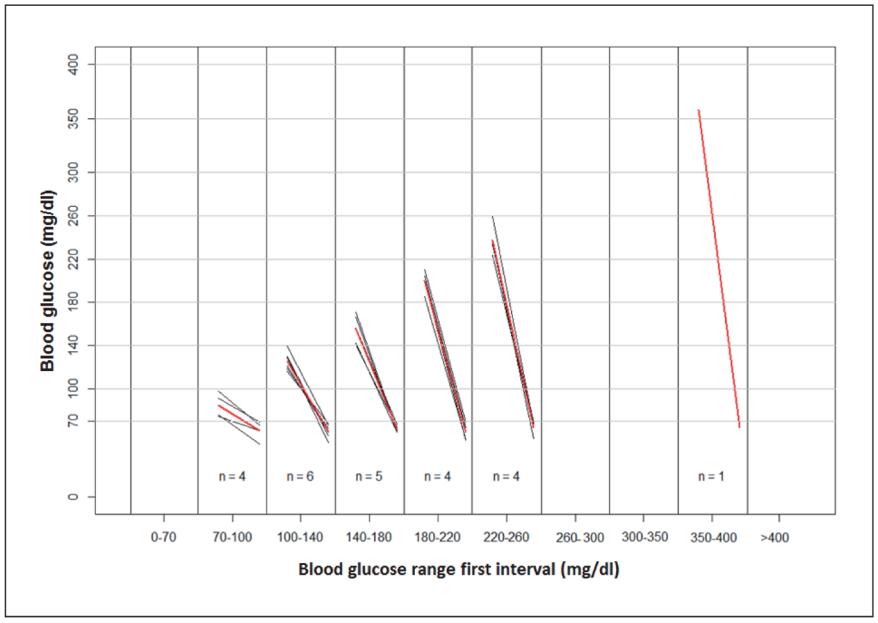

Fig. 3 Blood glucose values preceding low glycemic events (<70 mg/dl). Black lines denote changes of blood glucose values over the measurement interval that resulted in a blood glucose value <70 mg/dl. Red lines are averages

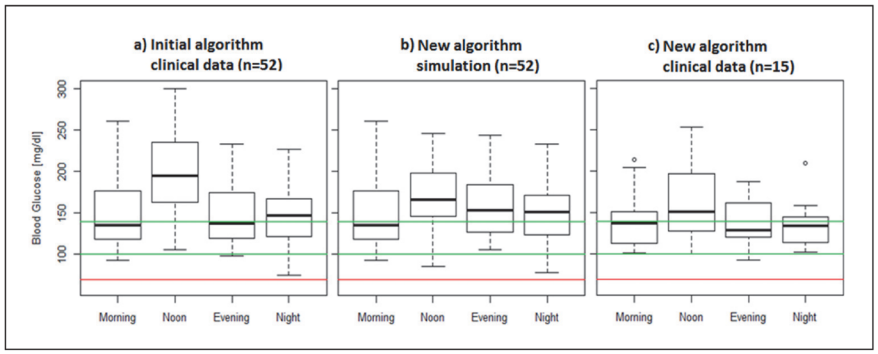

Fig. 4 Mean blood glucose per hospital stay – clinical data and simulation results

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Supplemental material

1. Initial insulin treatment protocol

Table AIII-1: Initial insulin treatment protocol

1. Basal Bolus Regimen with Insulin Glargine and Glulisine
1.A. Insulin Orders
• Discontinue oral antidiabetic drugs (sulfonylureas, repaglinide, nateglinide, metformin, pioglitazone, rosiglitazone, sitagliptin) and non-insulin injected antidiabetic medication (pramlinitide, exenatide) on admission.
• Starting insulin total daily dose (TDD): 0.5 units per kg of body weight.
• Reduce insulin TDD to 0.3 units per kg of body weight in patients ≥ 70 years of age and/or with a serum creatinine ≥ 2.0 mg/dL.
• Give half of total daily dose as insulin glargine and half as insulin glulisine.
• Give insulin glargine once daily, at the same time of the day.
• Give insulin glulisine in three equally divided doses before each meal. Hold insulin glulisine if patient not able to eat.
1.B. Supplemental insulin
• Give supplemental insulin glulisine following the "sliding scale" protocol (1E) for blood glucose > 140 mg/dl.
• If a patient is able and expected to eat all, give supplemental glulisine insulin before each meal and at bedtime following the "usual" column.
• If a patient is not able to eat, give supplemental glulisine insulin every 6 hours (6-12-6-12) following the "sensitive" column.
1.C. Insulin adjustment
• If the fasting and predinner BG is between 100 - 140 mg/dl in the absence of hypoglycemia the previous day: no change
• If the fasting and predinner BG is between 140 - 180 mg/dl in the absence of hypoglycemia the previous day: increase insulin TDD by 10% every day
• If the fasting and predinner BG is >180 mg/dl in the absence of hypoglycemia the previous day: increase insulin TDD dose by 20% every day
• If the fasting and predinner BG is between 70 - 99 mg/dl in the absence of hypoglycemia: decrease insulin TDD dose by 10% every day
• If a patient develops hypoglycemia (BG <70 mg/dL), the insulin TDD should be decreased by 20%.
1.D. Blood glucose monitoring. Blood glucose will be measured before each meal and at bedtime (or every 6 hours if a patient is not eating) using a glucose meter

Table AIII-2: Initial insulin treatment protocol – Supplemental insulin scale

	☐	☐	☐
Blood Glucose (mg/dL)	Insulin Sensitive	Usual	Insulin Resistant
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
> 400	14	16	18

** Check appropriate column below and cross out other columns

The numbers in each column indicate the number of units of glulisine or regular insulin per dose. Supplemental" dose is to be added to the scheduled dose of glulisine or regular insulin.

2. Structured Literature Search: Critical Appraisal

Keyword queries:

Pubmed search:

("Estimating glucose"[Title/Abstract] OR "glucose estimation" title/abstract OR "Predicting glucose"[Title/Abstract]) OR "glucose prediction"[Title/Abstract] OR "forecast glucose"[Title/Abstract] OR "glucose forecasting"[Title/Abstract] AND "diabetes"[Title] AND ("2012/01/01"[PDAT] : "2013/02/04"[PDAT])

IEEE Xplore metadata search:

(glucose prediction OR predicting glucose OR glucose estimation OR estimating glucose OR glucose forcast* OR forcasting glucose) AND diabetes

Filter: ("2012/01/01"[PDAT] : "2013/02/04"[PDAT])

Table AIII-3: Overview work: theses/books

Thesis / Book	Prediction algorithm /technology	Diabetes type	Glycemic source: CGM or capillary BG data	Forecast period	Algorithm tested in a clinical trial	Study population
2004 Peter Kok Predicting blood glucose levels of diabetics using artificial neural networks (Master Thesis)	NN	1	capillary BG	Next measurement	No	1
2011 Matthew T Wiley Machine Learning for Diabetes Decision Support (Master thesis)	Support Vector Regression, Autoregressive Integrated Moving Average	1	CGM	30, 60 min	No / pilot study	10
2011 Marzia Cescon Linear Modeling and Prediction in Diabetes Physiology (PhD thesis)	Autoregressive moving average with exogenous inputs, state-space models	1	capillary BG	Up to 120 min	No	9
2009 David Duke Intelligent Diabetes Assistant (PhD thesis)	Linear and Gaussian kernel	1 + 2	capillary BG	2h post prandial	No / pilot study	16
2012 Frederik Stahl Diabetes Mellitus Glucose Prediction by Linear and Bayesian Ensemble Modeling (PhD thesis)	Autoregressive model, ARMA	1	CGM	20,40,60 min	No	47
2011 Georga et al. Glucose Prediction in Type 1 and Type 2 Diabetic Patients Using Data Driven Techniques (Book chapter)	Compartment model + Support Vector Regression	1 + 2	CGM	15, 30, 60, 120 min	No	7

Table AIII-4: Critical appraisal: selected publications

Publication	Prediction algorithm /technology	Diabetes type	Glycemic source: CGM or capillary BG data	Forecast period	Algorithm tested in a clinical trial	Subjects
(Albisser, Baidal, et al. 2005) (Albisser, Sakkal, et al. 2005) (Albisser 2005)	Prediction engine in software: random walk techniques, mathematical models, simulation procedures. The methods are similar to the dynamic systems used in weather research and forecasting	1	capillary BG	Next interval	Yes	54
(Baghdadi & Nasrabadi 2007)	Radial basis function NN	1	capillary BG	Next interval	No	1
(Balakrishnan 2012)	multi-input single-output time series models	1	CGM	Short	No	12 children
(Bremer & Gough 1999)	Linear, non-linear, compartment model	1	CGM	10, 30 min	No	Summary of papers
(Briegel & Tresp 2002)	Non-linear state space model, NN, Monte-Carlo generalized EM(expectation maximization) algorithm	1	CGM	-	No	1
(Chemlal et al. 2011) (Chemlal et al. 2010)	Fit high order polynomial, Log-normal and Weibull distribution, Learning algorithm	2	-	Short	No	-
(Chernetsov et al. 2012) (Chernetsov et al. 2009)	NN	1	CGM	20,40,60,80, 100, 120 min	No	1
(Daskalaki et al. 2012)	AR, ARX, NN	1	CGM	30, 45 min	No	Virtual patients
(Eren-Oruklu et al. 2009)	AR, ARMA, forgetting factor	1+2	CGM	20, 30 min	No	30 healthy, 7 glucose-intolerant, 25 type II
(Eskaf et al. 2008)	NN	1	CGM	30 min	No	1
(Gani et al. 2009)	AR	1	CGM	<60 min	No	9
(Gani et al. 2010)	AR modelling universal models	1+2	CGM	30 min	No	Type I: 9 + 12 children

Publication	Prediction algorithm /technology	Diabetes type	Glycemic source: CGM or capillary BG data	Forecast period	Algorithm tested in a clinical trial	Subjects
						Type 2: 7
(Georga et al. 2012)	Random Forests	1	CGM	15, 30, 60, 120 min	No	27
(Georga et al. 2013)	Support Vector Regression	1	CGM	15, 30, 60, 120 min	No	27
(Hovorka et al. 2004)	Physiologic-oriented model	1	CGM	Up to 240 min	No	15 clinical experiments
(Iancu et al. 2009)	NN	1	CGM	Short	No	22 + 8 healthy subjects
(Lu et al. 2011)	AR	1 +2	CGM	20 min	No	34
(Mougiakakou et al. 2005)	Hybrid model, compartment + NN	1	capillary BG	Next measurement	No	1
(Otto et al. 2000)	Neural network, fuzzy system	1	capillary BG	Next measurement	No	-
(Pappada et al. 2011)	NN	1	CGM	75 min	No	10
(Percival et al. 2011)	multi-parametric model predictive control	1	CGM	3h	No	14 virtual patients
(Quchani & Tahami 2007)	NN, MLP, Elman	1	capillary BG	Long time	No	10
(Robertson et al. 2011)	NN	1	capillary BG	Next measurement	No	28 datasets from AIDA
(Rollins et al. 2010)	Block-oriented Wiener network	2	CGM	NA	No	1
(Shanthi 2012)	NN	1+2	CGM	30, 45 60 min	No	2 data sets
(Sparacino et al. 2007)	AR	1	CGM	Max 30 min	No	28
(Stahl & Johansson 2010)	Combined compartment system (glucose, insulin)	1	CGM	20, 40, 60 min	No	1
(Stahl & Johansson 2012)	Combination of multiple plasma glucose predictors	1	CGM	Up to 60 min	No	Simulated 20 data sets
(Stahl et al. 2012)	Bayesian combination of multiple plasma glucose predictors	1	CGM	20,40,60 min	No	12
(Valletta et al. 2009)	Gaussian processes	1	CGM	25, 60, 240 min	No	19
(Zainuddin et al. 2009)	NN, Wavelet, principal component analysis	1	capillary BG	Next interval	No	1
(Zecchin et al. 2012)	NN	1	CGM	Short	No	9 + 20 simulated

Publication	Prediction algorithm /technology	Diabetes type	Glycemic source: CGM or capillary BG data	Forecast period	Algorithm tested in a clinical trial	Subjects
(Zhao et al. 2012a)	Latent-variable-based statistical method	1	CGM	30 min	No	7
(Zhao et al. 2012b)	Multivariate statistical analysis	1	CGM	30 min	No	26

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