

# Prospective External Validation of an Algorithm Predicting Hourly Basal Insulin Infusion Rates from Characteristics of Patients with Type 1 Diabetes Treated with Insulin Pumps

## Authors

Jana S. Schmelzer<sup>1,2</sup>, Melanie Kahle-Stephan<sup>1,3</sup>, Juris J. Meier<sup>1,2</sup>, Michael A. Nauck<sup>1,3</sup>

## Affiliations

- 1 Diabetes, Endocrinology and Metabolism Section, Medical Department I, Katholisches Klinikum Bochum, St. Josef-Hospital, Klinikum der Ruhr-Universität Bochum, Bochum, Germany
- 2 Department of Internal Medicine, Augusta-Krankenanstalt gGmbH, Bochum, Germany
- 3 Diabetes Center Bad Lauterberg, Bad Lauterberg im Harz, Germany

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## Correspondence

Prof. Dr. med. Dr. h.c. Michael A. Nauck  
Diabetes, Endocrinology and Metabolism Section, Medical Department I, Katholisches Klinikum Bochum, St. Josef-Hospital (Ruhr University Bochum), Gudrunstr. 56 44791 Bochum  
Germany  
Tel.: +49 234/509-6332, Fax: +49 234/509-2714  
michael.nauck@rub.de

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## ABSTRACT

**Background** We previously published an algorithm predicting 24 h basal insulin infusion profiles in insulin pump-treated subjects with type 1 diabetes profiles from six subject characteristics. This algorithm was to be externally validated in an independent environment and patient population.

**Methods** Thirty-two patients with pump-treated type diabetes were switched to their individually algorithm-derived basal insulin infusion profile, and the appropriateness of fasting glycemic control was scrutinized by means of a supervised 24 h fast. Primary endpoint was appropriate fasting glycemic control according to pre-defined criteria in at least 80 % of the cohort.

**Results** In 24 out of 32 patients switching to the algorithm-derived basal insulin infusion rate and undergoing a 24-h fasting period, appropriate glycemic control was achieved (= 75 %, lower than the pre-defined threshold of 80 %), two patients discontinued the fast due to hyperglycemia, and six finished the fasting period, however, with inappropriate fasting glycemic control (entirely due to hyperglycemic episodes). There were no obvious differences in baseline characteristics between those with appropriate vs. inappropriate fasting glycemic control on the basal insulin infusion rate provided by the algorithm.

**Conclusion** In conclusion, when testing fasting glycemic control with an algorithm-derived individual basal insulin infusion profile during a 24 h fasting period in a cohort unrelated in terms of the hospital environment and catchment area, the success rate was lower than a pre-defined threshold for concluding utility of this algorithm. Therefore, applying this algorithm in order to initiate or optimize basal insulin infusion profiles in type 1 diabetes cannot be generally recommended.

## Introduction

Severe insulin deficiency in patients with type 1 diabetes necessitates insulin replacement therapy, which can be optimized by employing insulin pumps [1, 2]. Insulin pump treatment has the advantage of tailoring basal insulin infusion rates (BIIRs) to individual

needs [1, 2] rather than relying on the pharmacokinetics of basal insulin preparations. Previous work from our group has indicated prominent inter-individual heterogeneity in this respect [3], with some patients achieving appropriate glycemic control under fasting conditions with almost constant hourly basal insulin infusion

rates, while other patients need a basal insulin infusion profile with prominent diurnal changes, e. g., representing the “dawn” phenomenon (progressively increasing insulin needs between midnight and early morning hours) [4]. In a previous publication, we introduced an algorithm (based on multivariate regression analysis) allowing the prediction of individual basal insulin infusion rates from six anthropometric and laboratory parameters, which not only provides an estimate of the individual overall 24 h basal insulin needs but also addresses the diurnal “ups” and “downs” in hourly basal insulin infusion profiles, mainly applicable to predict a prominent vs. negligible “dawn” phenomenon (progressive rise in hourly basal insulin needs from approximately 1 to 7 am). This analysis was based on a cohort of 339 patients with type 1 diabetes using insulin pumps, randomly divided into an exploratory cohort and a confirmatory cohort in order to model individual BIIRs using multivariate regression analysis (exploratory cohort), and applying this model for the prediction of basal insulin infusion profiles in the confirmatory cohort [5]. This “internal” validation process suggested that the algorithm-derived basal insulin infusion rate will provide appropriate fasting glycemic control over and beyond the patient cohort providing data contributing to the multivariate regression model used to derive individual basal insulin infusion rates [5]. However, both the explanatory and the confirmatory cohorts were (mutually exclusive) random samples from the same patient population [5]. Thus, the question arises of how the same algorithm would perform in an independent population of patients with pump-treated type 1 diabetes. The present report summarizes our experience of applying this algorithm to predict individual basal insulin infusion profiles in a different environment. In principle, all participating patients were switched to the algorithm-derived basal insulin infusion profile, and fasting glycemic control was examined during a supervised 24 h fast on inpatient optimization of glycemic control.

## Patients and Methods

### Ethics committee approval

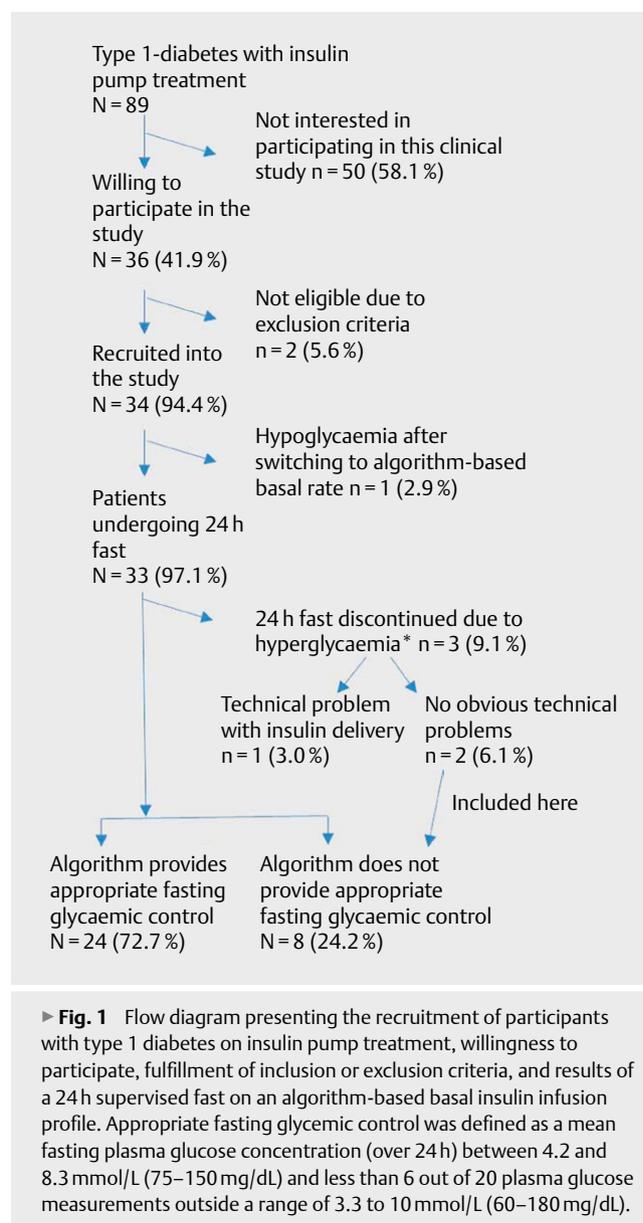
The present clinical study was approved by the ethics committee of the Medical Faculty of the Ruhr University Bochum (registration number: 18–6340, date: May 2, 2019). All patients gave their written informed consent before any study-related activity.

### Study design

Subjects with type 1 diabetes on insulin pump treatment were offered to switch from their empirically derived 24 h basal insulin infusion profiles to a published algorithm-derived 24 h basal insulin infusion profile calculated based on six relevant subjects characteristics and to participate in a supervised 24 h fast to determine, whether this algorithm-based basal insulin infusion profile provides appropriate fasting plasma glucose control according to pre-specified criteria.

### Selection of study patients

Patients were included in the present analysis if they had an unequivocal diagnosis of type 1 diabetes and were treated with con-



tinuous subcutaneous insulin infusion (CSII) (using any approved model of an insulin pump), and had an age of 18 years to 75 years (inclusive) and a body-mass-index of 16–60 kg/m<sup>2</sup>. Patients were excluded if their diabetes type was different from type 1 diabetes if they might have been pregnant at the time of inpatient treatment or if liver transaminases were more than threefold above the upper limit of normal, or if eGFR was below 45 mL/min (CKD-Epi equation). A flow chart describing the recruitment process, the participation in a 24 h supervised fast, and the results of fasting plasma glucose control on an algorithm-based basal insulin infusion rate are shown in ► **Fig. 1**. Data from a previous retrospective analysis of fasting plasma glucose control in pump-treated subjects with type 1 diabetes, which had been used for the generation of the multivariate regression model applied for the individual calculation of algorithm-derived basal insulin infusion rates, were used for comparing important clinical data [5].

## Algorithm to individually calculate hourly basal insulin infusion profiles

Algorithm-derived hourly basal insulin infusion profiles were calculated as described in detail previously [5], using age, gender, body-mass-index, the duration of insulin pump treatment, glycated hemoglobin (HbA<sub>1c</sub>), and serum triacylglycerols as input variables. The output provided a basal insulin infusion rate for each hour of the day. Patients consenting to the participation in the present study were switched from their empirically derived baseline basal insulin infusion rate to the individually algorithm-derived basal insulin infusion rate for a duration of at least 24 h, before the initiation of 24 h supervised fasts at 6 pm. During this period, plasma glucose was frequently measured to ascertain acceptable glycemic control with this algorithm-derived basal insulin infusion rate in order to minimize the risk for hypoglycemic or hyperglycemia in response to an altered basal insulin infusion rate. A single patient developed several episodes of hypoglycemia during the night and it was decided not to start the supervised fast in this patient.

## Change of insulin infusion catheters before 24 h supervised fasts

The insulin infusion catheters used depended on the type of insulin pump used. Catheters were generally changed every 2 days. The prospective injection site was checked for inflammation and induration. The decision on the catheter insertion site was jointly made by healthcare professionals and the patient.

## 24 h supervised fasting tests to test the appropriateness of algorithm-based basal insulin infusion profiles

Supervised fasts were performed in a standardized manner over 24 hours, starting at 6 pm, omitting dinner, breakfast, and lunch, or any snacks in between, unless carbohydrate intake was necessary to compensate for low plasma glucose values or hypoglycemia (plasma glucose < 3.3 mmol/L or 60 mg/dL; 150 mL apple juice equivalent to 15 g of rapidly absorbed carbohydrate). Fasting was discontinued at 6 pm of the next day. During this period, capillary samples for the determination of plasma glucose were obtained at 6, 7, 8, 9, 10, 11 pm, at 2, 5, 7, 8, 9, 10, 11, 12 am, and at 1, 2, 3, 4, 5, and 6 pm. In addition, capillary blood samples for the determination of ketone bodies were taken at 6 and 11 pm and at 8 and 12 am, as well as at 6 pm of the next day.

## Individual criteria for the appropriateness of fasting plasma control during 24 h fasts on the algorithm-based basal insulin infusion rate

Since there are no generally accepted standards to judge plasma glucose concentrations during 24 h fasting periods, we derived our criteria from a large database on 24 h fasting tests in subjects with type 1 diabetes using insulin pumps, based on which criteria predicted changes in basal insulin infusion rates recommended by health care professionals or not. According to these criteria, appropriate fasting glycemic control was defined as a mean fasting plasma glucose concentration (over 24 h) between 4.2 and 8.3 mmol/L (75–150 mg/dL) and less than 6 out of 20 plasma glucose measurements outside a range of 3.3 to 10 mmol/L (60–180 mg/dL).

## Criteria to decide on the overall appropriateness of fasting glucose control with algorithm-derived basal insulin infusion rates

It was pre-specified that the algorithm-derived basal insulin infusion profile should be considered appropriate if the individual criteria for fasting plasma glucose control outlined above would be fulfilled by at least 80 % of the cohort, with a lower bound of the 95 % confidence interval of  $\geq 60$  %. An interim analysis was planned after 30 patients. Another 20 patients were planned to be recruited in the case that the current proportion with appropriate fasting plasma glucose control was below 80 %. At the time of the planned interim analysis, the results of which are reported in the present manuscript, the required proportion with appropriate fasting plasma glucose control was not achieved. At this time (August 2020), patient attendance at our specialized diabetes division was considerably reduced due to the SARS-CoV-2 pandemic, and it was considered impossible to recruit another 18 patients with reasonable effort and within a reasonable period of time. Therefore, it was decided to stop recruitment and analyze the results of the current clinical study with the number of patients enrolled up to this time.

Continuous glucose monitoring was used in individual patients at their discretion (approximately 50 %), however, without allowing any algorithms impacting insulin delivery or glycemic control (e. g., low glucose suspension). The results of continuous glucose monitoring were not analyzed as part of the protocol.

## Measurement of HbA<sub>1c</sub>

To assess the impact of appropriate vs. non-appropriate control of fasting plasma glucose during 24 h supervised fasts on overall glycemic control, we measured HbA<sub>1c</sub> at screening and 3 months later, taking blood at their homes.

## Laboratory measurements

Capillary plasma glucose was determined immediately after obtaining the blood specimens using an Accu-Chek Inform II device (Roche Diagnostics Deutschland GmbH, 68305 Mannheim, Germany). Ketone bodies were determined in venous blood using a “Freestyle Precision  $\beta$ -ketone” Blutketon T test strips read out using a FreeStyle Precision Neo handheld device (Abbott GmbH, 65205 Wiesbaden, Germany).

## Calculations

For each participant, the mean glucose concentration during the supervised fast was calculated, and the number (proportion) with a mean fasting plasma glucose outside the target range (4.2 to 8.3 mmol/L or 75 to 150 mg/dL) was determined. Also, for each participant, the number and proportion [%] of plasma glucose concentrations above and below the range defined for appropriate fasting glucose control for individual measurements (3.3 to 10.0 mmol/L or 60 to 180 mg/dL) was calculated. Next, the number of values falling outside this range was determined for each participating subject. If this number (proportion) was above 6 (30.0 %), fasting plasma glucose control was considered inappropriate with the algorithm-based basal insulin infusion profile for this subject. The number of subjects with inappropriate fasting plasma glucose control was related to the total number of patients examined to decide

whether the present study provided validation for using this algorithm-derived basal insulin infusion profile.

Patient characteristics were compared between subjects with appropriate and inappropriate fasting plasma glucose control on the algorithm-derived basal insulin infusion profile. Since the algorithm was derived from data provided by a different cohort of patients and had been internally validated within a randomized “confirmatory” subpopulation from the sample used to derive the algorithm (“prospective” subpopulation), patient characteristics were also compared between the present cohort (used for external validation of the algorithm) and the “confirmatory” subpopulation used for the internal validation as published previously [5].

## Statistical analysis

Patient characteristics are reported as means  $\pm$  standard deviation (SD) or counts, and results are reported as means  $\pm$  standard error of the mean (SEM). Significances of differences between two categories (e. g., patient cohorts) were tested by one-way analysis of variance (continuous variables) or contingency table analysis (Fisher’s exact test for  $2 \times 2$  contingency tables (categorical variables). Significances of differences in glucose concentrations serially determined over time were tested by repeated-measures analysis of variance. The subpopulation (e. g., subjects achieving appropriate vs. inappropriate fasting plasma glucose control with the algorithm-derived basal insulin infusion profile) was used as a fixed independent variable. Results are reported as p-values for (A) by the group, (B): over time, and (AB): by the interaction of group and time. If a significant difference according to the category or a significant interaction of category and time was documented ( $p < 0.05$ ), one-way ANOVA was used to detect significant differences at specific time points. P-values  $< 0.05$  were taken to indicate significant differences.

## Results

### The primary endpoint and patient flow diagram

The primary aim of the current study was to define the proportion of patients in whom the algorithm-derived basal insulin infusion rate profile provided appropriate fasting glucose control during a 24 h fast according to pre-defined criteria (see methods section). Patient flow throughout the study is depicted in ► **Fig. 1**, with reference to the question whether appropriate fasting glycemic control was achieved or not. Of the 33 patients eligible and willing to participate in the 24 h fast, appropriate fasting glycemic control was achieved in 24 (72.7%). Of the remaining nine patients, one developed hypoglycemia before the 24 h fast while already delivering the basal insulin infusion rate calculated by the algorithm. However, since this patient was using meal-related boluses during this period, it remained unclear whether this was related to the basal rate. One additional patient developed hyperglycemia due to obvious technical problems (clotted tubing), such that this patient was not counted as a failure of the algorithm-based basal insulin infusion rate profile. In 8 patients, hyperglycemia occurred during the 24 h fast, indicating inappropriate fasting glycemic control with the algorithm-derived basal rate. Overall, the algorithm-derived

basal rate provided appropriate fasting glycemic control in 24 out of 32 patients undergoing the 24 h fast, which is 72.7% of those starting the 24 h fast. When excluding the single patient with technical problems related to pump-derived insulin delivery, this percentage rose to 75.0%. Our pre-defined criterion for the overall success of algorithm-derived basal rate profiles was appropriate fasting glycemic control in at least 80 percent. Thus, compared to pre-defined criteria, our study does not provide evidence for an overall successful provision of appropriate fasting glycemic control by our algorithm-derived basal insulin infusion rate.

### Patient characteristics

When comparing the patient characteristics of those subjects, who achieved appropriate glycemic control with the algorithm-derived basal insulin infusion rate versus those who did not, there was a trend towards a better baseline HbA<sub>1c</sub> and a significantly higher eGFR (with both mean values in the normal range) in those failing on the algorithm-derived basal insulin infusion rate, and a 55.5% higher 24 h basal insulin infusion rate, while typical anthropometric and laboratory markers of insulin resistance (body-mass-index, triglycerides, and liver enzymes) showed more favorable results in those failing to achieve appropriate fasting glycemic control with the algorithm-derived basal insulin infusion rate. Otherwise, there were no remarkable differences (► **Table 1**).

### Plasma glucose profiles and basal rate tests (24 h fasts) on individually algorithm-derived basal insulin infusion rates

When assessing plasma glucose concentrations throughout the 24 h period (6 pm to 6 pm) of the supervised fast, it is obvious that those achieving appropriate fasting glycemic control with the algorithm-derived basal insulin infusion rate had mean plasma glucose concentrations within the target ranges for individual fasting plasma glucose concentrations (3.3–10.0 mmol/L or 60 to 180 mg/dL) as well as within the target range for mean fasting plasma glucose concentrations (4.2–8.3 mmol/L/75–150 mg/dL; ► **Fig. 2a**). Those not achieving appropriate fasting glycemic control with the algorithm-derived basal insulin infusion rate developed frankly hyperglycemic fasting plasma glucose concentrations (► **Fig. 2a**). When looking at the proportion of patients experiencing hyperglycemic ( $> 10$  mmol/L or  $> 180$  mg/dL; ► **Fig. 2b**) or hypoglycemic ( $< 3.3$  mmol/L or  $< 60$  mg/dL) fasting plasma glucose concentrations at individual time points, those with appropriate fasting glycemic control with the algorithm-based basal insulin infusion rate had a balanced occurrence of both hyper- and hypoglycemia (up to 10 and 15% of this sub-cohort) over the 24 h period, while in those with inappropriate fasting glycemic control, there was no single incident of hypoglycemia (► **Fig. 2c**), but hyperglycemia in 35 to almost 100% of this sub-cohort, peaking in the early afternoon hours (► **Fig. 2b**). Plasma ketone body concentrations were significantly higher in those with inappropriate fasting plasma glucose control (► **Fig. 2d**). In both subgroups, there was a trend towards increasing ketone body plasma concentrations with a longer duration of the fast.

► **Table 1** Subject characteristics of the type 1-diabetic patients treated with insulin pumps participating in the present study grouped by whether the algorithm-based basal rate provided appropriate or inappropriate glycemic control

Cohort	Unit	Appropriate fasting glucose control (n = 24)	Inappropriate fasting glucose control (n = 8)	Significance p-value
Age	[years]	41.0 ± 12.6	36.4 ± 11.6	0.37
Sex	Female/male (% female)	14/10 (58.3)	3/5 (37.5)	0.42
Body-Mass-Index	[kg/m <sup>2</sup> ]	27.8 ± 4.9	25.5 ± 4.8	0.29
Duration of Type 1 diabetes	[years]	19.5 ± 10.6	18.8 ± 9.1	0.85
Duration of insulin pump treatment	[years]	6.5 ± 6.6	10.7 ± 6.1	0.29
HbA <sub>1c</sub>	[%]	8.9 ± 1.2	8.6 ± 1.7	0.078
Triglycerides	[mg/dL]	125.9 ± 107.3	119.5 ± 59.0	0.87
Alanine aminotransferase	[U/L]	28.8 ± 21.5	25.3 ± 15.0	0.67
γ-glutamyl transpeptidase	[U/L]	30.3 ± 52.6	30.8 ± 44.3	0.98
eGFR	[mL/min]	91.6 ± 20.6	113.1 ± 17.6	0.013
RR <sub>systolic</sub>	[mmHg]	128.5 ± 7.9	128.8 ± 6.9	0.95
RR <sub>diastolic</sub>	[mmHg]	77.7 ± 5.3	76.9 ± 5.2	0.70
Prevalence of arterial hypertension	yes/no (% yes)	9/15 (37.5)	2/6 (25.0)	0.68
Frequency of any hypoglycaemia	yes/no (% yes)	2.7 ± 2.5	2.3 ± 2.3	0.60
Frequency of severe hypoglycaemia	yes/no (% yes)	0.3 ± 1.1	0.4 ± 0.5	0.84
Prevalence of retinopathy	yes/no (% yes)	4/20 (20.0)	4/4 (50.0)	0.15
Prevalence of nephropathy	yes/no (% yes)	7/17 (29.2)	2/6 (25.0)	> 0.99
Prevalence of neuropathy	yes/no (% yes)	5/19 (20.8)	1/7 (12.5)	> 0.99
Prevalence of coronary disease	yes/no (% yes)	0/24 (0.0)	0/8 (0.0)	> 0.99
Prevalence of diabetic foot syndrome	yes/no (% yes)	0/24 (0.0)	0/8 (0.0)	> 0.99
24 h basal insulin infusion rate	[IU per day]	21.1 ± 7.7	32.8 ± 12.1	0.0034
	[IU/ kg BW per day]	0.24 ± 0.09	0.38 ± 0.09	0.0008

Mean ± standard deviation for continuous variables and number fulfilling and not fulfilling a given criterion (proportion fulfilling this criterion) for categorical variables; eGFR: Estimated glomerular filtration rate (CKD-Epi equation); RR: Blood pressure according to Riva-Rocci

### Comparison of basal insulin infusion rates at baseline, after switching to the algorithm-derived basal insulin infusion rate, at hospital discharge, and after adjusting basal insulin infusion rates according to experiences from everyday life

In the subgroup achieving appropriate fasting glycemic control with the algorithm-derived basal insulin infusion rate, switching to the algorithm-derived basal insulin infusion rate slightly increased basal insulin infusion, in particular during the period corresponding to the “dawn” phenomenon, overall, by  $3.3 \pm 1.1$  (mean ± SD) IU per 24 h or 13.6%. Minor changes were introduced in response to the results of the 24 h fast, and empirically, during the months following hospital discharge, the changes introduced by the algorithm tended to be reversed again (**Supplementary Figure 2**). In those not achieving appropriate fasting glycemic control with the algorithm-derived basal rate, the 24 h basal insulin infusion rate at baseline was significantly higher, and the 24 h profile did not display a gradually increasing basal insulin infusion rate during the night hours (corresponding to a putative “dawn” phenomenon; **Supplementary Fig. 2**). Switching to the algorithm-derived basal insulin infusion rate restored the expected 24 h profile with an accentuated rise in basal insulin delivery corresponding to a “dawn” and “dusk” phenomenon. Overall, this transition reduced 24 h insulin delivery by  $8.8 \pm 3.4$  IU (mean ± SD) or 26.9%. The main difference between subgroups achieving appropriate fasting glucose control with the algorithm-derived basal insulin infusion rate or not was a rise in 24 h basal insulin delivery rates induced by the algo-

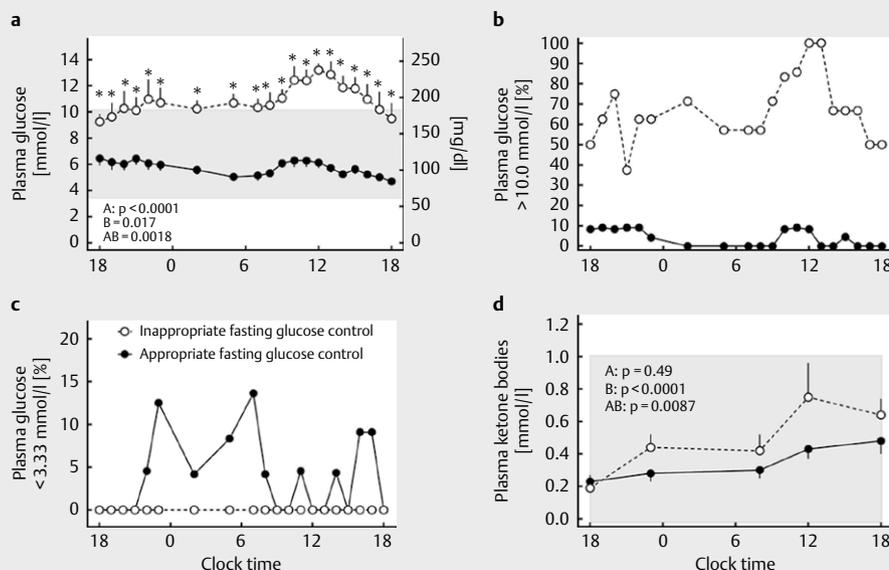
rithm in those with appropriate and a major reduction in those with inappropriate fasting glycemic control (► **Fig. 3**), with relatively minor changes in 24 h basal insulin delivery rates before hospital discharge or during the 3 months following inpatient treatment.

### Glycated hemoglobin at baseline and 3 months following inpatient optimization of basal insulin infusion profiles

HbA<sub>1c</sub> was reduced by  $1.0 \pm 0.9\%$  in 20 out of 24 (83.3%) with appropriate fasting glycemic control within approximately 3 months following the attempt to optimize basal insulin infusion profiles with the help of our algorithm, but also by  $1.4 \pm 1.5$  in the 4 patients available for providing a blood sample to measure HbA<sub>1c</sub> 3 months later (in 4 out of 8 patients, 50.0%) (► **Fig. 3**).

### Discussion

The present study was undertaken to provide external validation of a previously published algorithm [5], which provides individual estimates for the 24 h basal insulin infusion profile regarding both the overall 24 h basal insulin needs and its distribution across the 24 hours of the day, and the degree of diurnal variability, e. g., related to the “dawn” phenomenon. In contrast with an “internal” validation, which had suggested appropriate fasting plasma glucose control with this algorithm-derived basal insulin infusion rate [5], the present study, performed in a totally different environment,



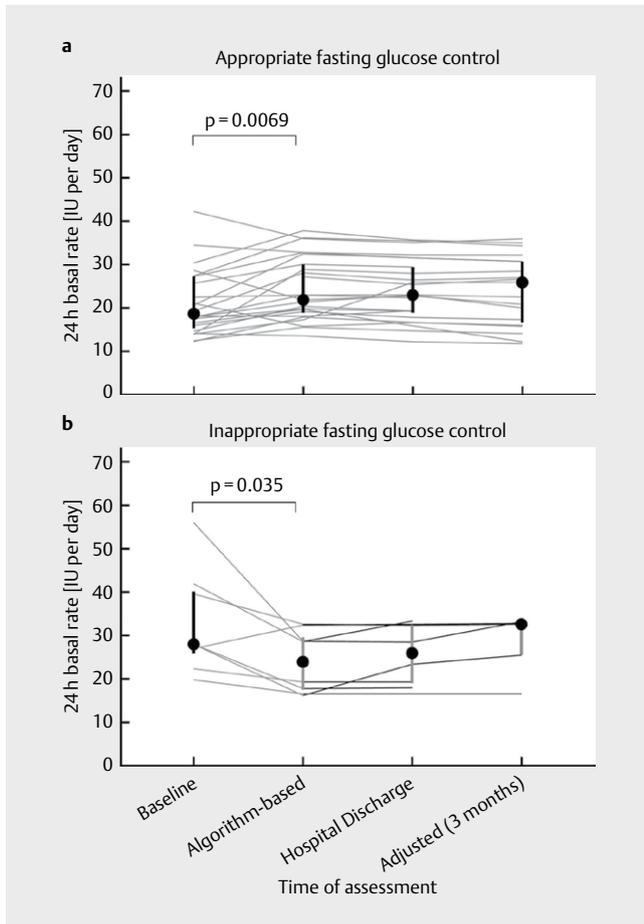
► **Fig. 2** Plasma glucose and ketone body concentration profiles during a 24 h supervised fast on an algorithm-based basal insulin infusion profile in subjects with type 1 diabetes either achieving appropriate fasting plasma glucose control or not. For the definition of appropriate fasting glycemic control, see the methods section. Twenty-four subjects had achieved appropriate fasting glucose control (full circles), and eight subjects had inappropriate fasting glucose control (open circles) with the algorithm-based 24 h basal insulin infusion profile. (a) Plasma glucose concentrations. (b) The proportion of patients exceeding pre-defined upper limits of an appropriate range of glucose concentrations for single measurements ( $> 10.0$  mmol/L or 180 mg/dL). (c) The proportion of patients with plasma glucose concentrations below pre-defined lower limits of an appropriate range of glucose concentrations for single measurements ( $< 3.33$  mmol/L or 65 mg/dL). The ranges considered appropriate for single measurements and individual mean plasma glucose concentrations are shown as lightly and intermediately shaded grey areas in panel A, respectively. (d) Ketone body concentrations. Mean  $\pm$  standard error of the mean or proportions (%). Results of repeated-measures-ANOVA are reported as p-values for A: by the patient group; B: regarding changes over time; and AB: for the interaction of group assignment and time. Asterisks indicate a significant difference ( $p < 0.05$ ) for individual time points.

does not confirm the general usefulness of applying our algorithm for the optimization of basal insulin infusion rates.

The criteria we pre-specified for judging the appropriateness of basal insulin dosage were based on clinical experience and the analysis of a large database of 24 h supervised fasts. By defining proportions of plasma glucose values inside and outside of pre-defined concentration ranges, our method is somewhat similar to the “time in tighter range (70–140 mg/dL)” used in conjunction with continuous glucose measurements, as suggested by Battelino et al. 2023 [6].

While there was a subgroup within our prospective cohort which achieved appropriate control by applying this algorithm, it only represented 72.7% of those participating in the 24 h supervised fast, or at most 75.0%, if a patient with obvious technical problems related to pump-derived insulin delivery was neglected in this calculation (► Fig. 1). Our ambition had been to observe whether the algorithm-derived basal insulin infusion rate profile provides appropriate fasting plasma glucose control in 80 or more percent of the total cohort, which was not achieved. Furthermore, those with inappropriate fasting plasma glucose control developed frank hyperglycemia with a significant rise in ketone body concentrations (► Fig. 2), indicating insufficient insulin delivery throughout the 24 h fasting period. Remarkably, in this sub-cohort with inappropriate fasting glycemic control, the algorithm suggested a substantial reduction in 24 h basal insulin needs when compared to their

previous, empirically derived 24 h basal insulin delivery rate (Supplementary Figure 2), which was significantly higher than in those achieving appropriate glycemic control with the algorithm-derived basal rate (► Table 1). Other clinical, anthropometric, or laboratory parameters compared between those with appropriate and inappropriate fasting glycemic control were not significantly different (► Table 1). In particular, the six patient characteristics providing input into our algorithm to predict individual basal insulin infusion profiles (age, sex, body-mass-index, duration of insulin pump treatment, HbA<sub>1c</sub>, triglycerides) did not differ significantly between the two sub-cohorts with appropriate and inappropriate fasting glycemic control with the algorithm-derived basal insulin infusion profile. Those with inappropriate fasting glycemic control tended to have lower age and a higher proportion of male subjects (both predicting a higher basal insulin need according to our algorithm) but had a lower body-mass-index, a longer duration of insulin pump treatment, a lower HbA<sub>1c</sub> and lower triglycerides at baseline. All these latter trends would generate lower 24 h insulin requirements when applying our algorithm [5]. In retrospect, it is no surprise that these minor differences in patient characteristics do not result in estimates of 24 h basal insulin requirements that are compatible with the factual differences between the two groups of patients. In other words, there appear to be confounders with a substantial influence on the individual basal insulin infusion profile, which are not picked up by our algorithm. In the absence of signif-



► **Fig. 3** 24 h basal insulin infusion rates [IU/ d] at baseline, after switching to the algorithm-based basal rate profile, at the time of hospital discharge, and after adjustments prompted in response to everyday experiences (approximately 3 months after the 24 h supervised fast with the algorithm-based basal rate profile) in subjects with type 1 diabetes either achieving appropriate fasting plasma glucose (n = 24) control or not (n = 8). P-values present the difference between the total 24 h basal insulin administered at baseline and after switching to the algorithm-based basal insulin infusion profile. At baseline, the total 24 h basal insulin administered differed significantly ( $p = 0.0034$ ) between the groups achieving appropriate fasting plasma glucose control (n = 24) or not (n = 8).

icant differences regarding patient characteristics (► **Table 1**), these confounders remain elusive. The fatty liver disease could be a plausible candidate since it is associated with insulin resistance also in type 1 diabetes [7, 8] (which should translate into higher insulin needs), but serum liver transaminases were not different between the two groups, so this assumption is not supported by our data. The same consideration should apply to the effects of other ectopic fat depots, especially in the muscle [9, 10], and of physical exercise on insulin sensitivity [11, 12].

There also were only minor differences in patient characteristics between the patients studied in the present analysis as compared to those of the original cohort providing data to the multivariate regression model used for the individual prediction of basal insulin infusion profiles (**Supplementary Table 2**). In the present cohort, the duration of insulin pump treatment was significantly longer,

which would predict a lower 24 h basal insulin need according to our algorithm. Serum triglycerides were higher for the present cohort, which would lead to a higher estimate of 24 h basal insulin needs according to our algorithm. Thus, there was no obvious difference in the subject characteristics comparing the internal validation cohort and the present external validation cohort.

In the present study, a single patient was recruited who started his insulin pump therapy with a basal insulin infusion rate derived using our algorithm. He achieved appropriate fasting glycemic control. In our previous internal validation study, 67 patients were studied in the context of initiating insulin pump treatment, while 97 patients had previous insulin pump treatment and could rely on empirically optimized basal insulin infusion profiles. There were neither differences in the overall basal insulin need between beginners and experienced pump users, nor did this lead to differences in plasma glucose concentrations throughout the 24 h fast (details not shown), thereby ruling out this factor as a major confounder explaining the split results obtained in the present external validation study.

Originally, our protocol planned an interim analysis after having studied 30 patients. Had the success rate (percentage of patients achieving appropriate fasting glycemic control with the algorithm-derived basal insulin infusion rate profile) been high enough ( $\geq 80\%$ ), we would have considered this as a proof of the utility of our algorithm, which then could have been more generally recommended as part of the clinical management of insulin pump-treated patients with type 1 diabetes. With a slightly lower success rate, we had intended to study another 20 patients. The interim analysis (reported here), however, not only provided a success rate lower than necessary to conclude the utility of the algorithm, but it also showed that a proportion of the patients demonstrated hyperglycemia during fasting when applying this algorithm, with mean fasting plasma glucose concentrations of  $11.2 \pm 1.8$  mmol/L or  $202 \pm 31$  mg/dL, outside the pre-defined target ranges not only for the individual but also mean plasma glucose concentrations. As depicted in ► **Fig. 2b**, hyperglycemia  $> 10$  mmol/L or 180 mg/dL was diagnosed in the majority of patients in this subgroup at most time points during the 24 h supervised fast. Conversely, not a single episode of hypoglycemia was observed in this group, while in those with appropriate fasting glycemic control, a balance of only a few hyperglycemic and similarly rare hyperglycemic episodes were detected (► **Fig. 2**). In other words, using this algorithm appears to harm fasting glycemic control in the sub-population with inappropriate fasting glycemic control when using our algorithm, which is of sufficient size to require attention when drawing an overall conclusion from the present study. This was one reason why we decided to terminate the present study without recruiting additional patients. The other reason was a substantial delay in patient recruitment during the COVID-19 pandemic.

The present as well as our previous studies were designed to develop a simple algorithm to predict individual hourly insulin requirements in patients on insulin pump therapy in the absence of additional measures to adjust basal insulin delivery to the current metabolic needs, like “low-glucose suspend” [13] or “closed-loop algorithms” [14] making use of continuous glucose monitoring. However, we believe that a reasonably individualized basal insulin

delivery rate should contribute to an optimized treatment even when using sensor-augmented insulin pump treatment.

The present study was conducted in a specialized diabetes inpatient setting and demonstrates marked and consistent improvements in long-term glycemic control (as indicated by the reduction in mean HbA<sub>1c</sub> levels), which were achieved under such conditions in a selected group of patients, even despite recommending an inappropriate basal insulin infusion rate, at least in those patients in whom our algorithm failed (**Supplementary Figure 6**).

Our study has limitations: The overall number of patients examined (n = 32) may have been too low to reliably estimate the success rate regarding fasting glycemic control with the algorithm. There was no way of ascertaining compliance with the protocol, e. g., stringent fasting during the experimental 24 h fasting period. Insulin pumps were not read out to confirm the hourly basal insulin infusion rate to be identical with the algorithm-derived one after the fasts. Plasma insulin concentrations were not measured, which could have helped detect potential differences in insulin elimination kinetics (clearance) between those in whom the algorithm provided appropriate or inappropriate fasting glycemic control. However, we do not believe that these limitations had a substantial impact on our main conclusions.

In conclusion, when testing fasting glycemic control with an algorithm-derived individual basal insulin infusion profile during a 24 h fasting period in a cohort unrelated in terms of the hospital environment and catchment area, the success rate was lower than a pre-defined threshold for concluding the utility of this algorithm. Therefore, applying this algorithm in order to initiate or optimize basal insulin infusion profiles in type 1 diabetes cannot be generally recommended.

## Author contributions

JSS, JJM, and MAN designed the study; JSS recruited patients, supervised clinical procedures, and analyzed clinical data from hospital charts. MAN, MK-S, and JSS analyzed data and performed the statistical analysis. MAN and JSS drafted the manuscript. All authors have seen and approved the final version of this manuscript and have decided to submit it for publication. MAN is the guarantor who takes full responsibility for the work as a whole, including study design, access to data, and the decision to submit and publish the manuscript.

## Data availability

The data gathered in the present study are available in the form of Excel spreadsheets upon reasonable request to the corresponding author.

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## Conflict of Interest

MAN has been a member of advisory boards or has consulted with Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, Novo Nordisk, Pfizer, Regor, and ShouTi. He has received grant support from Eli Lilly & Co., Merck, Sharp & Dohme, and Novo Nordisk. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Centrix, Eli Lilly & Co., Menarini/Berlin Chemie, Medscape, Medical Learning Institute, Merck, Sharp & Dohme, and Novo Nordisk. JJM has received consulting and speaker honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Sharp & Dohme, Novo Nordisk, and Sanofi. He has received research support from Eli Lilly, Boehringer-Ingelheim, Merck, Sharp & Dohme, Novo Nordisk, Novartis, and Sanofi. MK-S, AML, and SW, have nothing to declare.

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