Adjusting insulin doses in patients with type 1 diabetes who use insulin pump and continuous glucose monitoring: Variations among countries and physicians

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Abstract

Aims
To evaluate physicians' adjustments of insulin pump settings based on continuous glucose monitoring (CGM) for patients with type 1 diabetes and to compare these to automated insulin dose adjustments.

Methods
A total of 26 physicians from 16 centres in Europe, Israel and South America participated in the study. All were asked to adjust insulin dosing based on insulin pump, CGM and glucometer downloads of 15 patients (mean age 16.2 ± 4.3 years, six female, mean glycated haemoglobin 8.3 ± 0.9% [66.8 ± 7.3 mmol/mol]) gathered over a 3-week period. Recommendations were compared for the relative changes in the basal, carbohydrate to insulin ratio (CR) and correction factor (CF) plans among physicians and among centres and also between the physicians and an automated algorithm, the Advisor Pro (DreaMed Diabetes Ltd, Petah Tikva, Israel). Study endpoints were the percentage of comparison points for which there was full agreement on the trend of insulin dose adjustments (same trend), partial agreement (increase/decrease vs no change) and full disagreement (opposite trend).

Results
The percentages for full agreement between physicians on the trend of insulin adjustments of the basal, CR and CF plans were 41 ± 9%, 45 ± 11% and 45.5 ± 13%, and for complete disagreement they were 12 ± 7%, 9.5 ± 7% and 10 ± 8%, respectively. Significantly similar results were found between the physicians and the automated algorithm. The algorithm magnitude of insulin dose change was at least equal to or less than that proposed by the physicians.

Conclusions

Physicians provide different insulin dose recommendations based on the same datasets. The automated advice of the Advisor Pro did not differ significantly from the advice given by the physicians in the direction or magnitude of the insulin dosing.

1 INTRODUCTION

Insulin dose adjustments are an important part of the diabetes management needed to achieve target glycaemic control, as insulin dose requirements change frequently.[1] These adjustments are based mainly on detailed glucose data: capillary blood glucose and/or continuous glucose monitoring (CGM) data, and insulin delivery and meal data, such as carbohydrate intake. The increasing use of insulin pumps and CGM enables easy gathering of these valuable data from the devices.

Indeed, the number of patients who use insulin pump therapy is constantly growing and, currently, it is estimated that more than a million patients around the world use this treatment method.[2] According to the Type 1 Diabetes Exchange registry, 50% of patients with type 1 diabetes in the United States use insulin pump therapy.[3] The rate of pump use is similar in Europe, with some centres reaching rates between 70% and 93%.[4] Studies have shown that insulin pump therapy may be associated with improved overall metabolic control compared with multiple daily injections, improved glycated haemoglobin (HbA1c) levels[5, 6] and reduced rates of severe hypoglycaemia.[5-7]

Optimal utilization of pump therapy requires the studying and application of a combination of theoretical knowledge and practical skills from all stakeholders, including the treating physicians, the diabetes educators, the patients and their caregivers. There is an ongoing need to tailor the pump settings, namely, the insulin correction factors (CFs), carbohydrate to insulin ratios (CRs), basal plan and insulin activity time, in order to optimize and improve glucose control. Retrospective analysis of CGM data can be a valuable means of guiding adjustments of these pump settings.[8] Nevertheless, analysis of this multitude of information may be overwhelming for many patients, caregivers and healthcare providers, as it requires extensive training and considerable time. Furthermore, there are limited data and no uniform guidelines to direct prescribers and patients regarding ways to optimize the parameters of the insulin pump settings and CGM.[9, 10] The lack of concrete guidelines leads to dose adjustments being made subjectively by healthcare professionals, which are based mostly on their individual experience and therefore greatly variable.

Diabetes care faces tremendous changes, as new technologies are emerging to help patients and healthcare providers cope better with daily tasks. These technological improvements include new apps, connected devices, medical platforms, big data and health analytics and decision support algorithms. Their incorporation into management paradigms may improve diabetes control, and patients' health and quality of life.[11]

Insulin and glucose data can be analysed by sophisticated algorithms and by artificial intelligence in order to detect individual glucose patterns as well as pitfalls in diabetes management and to suggest lifestyle and insulin dosing adjustments accordingly. The use of design support algorithms and telemedicine are emerging as tools to help adjust insulin dosing during and between visits.[8, 12, 13]

The Advisor Pro (DreaMed Diabetes Ltd, Petah Tikva, Israel), is a decision support software device, designed to assist healthcare professionals in decision-making when treating patients with type 1 diabetes who use insulin pump therapy and monitor their glucose levels using CGM. The Advisor Pro analyses data from various devices (CGM device, glucometer and insulin pump) and provides recommendations for insulin pump dosing adjustments, including a basal plan, CR plan and CF plan. In addition, it provides behavioural recommendations related to the way the patient delivers insulin and manages diabetes. The Advisor Pro has been clinically tested in a feasibility study. This was a single-centre study that included 13 patients with type 1 diabetes who used insulin pumps and CGM. Patients were randomly assigned to participate either in a group in which insulin pump adjustments were guided by a physician (control group) or a group that was guided by the Advisor Pro (intervention group). Insulin titration was performed every 3 weeks and endpoints were measured at the end of 3 months' intervention. No difference was found in the average time within range (70-180 mg/dL) and time in hypoglycaemia (<70 mg/dL) between the two groups at the end of the study. The proportion of time spent within range for the intervention group was 52% at baseline and 57% after 3 months, and in the control group it was 57% both at baseline and after 3 months. The time spent in hypoglycaemia decreased from 3.4% at baseline to 2.5% at the end of the study for the intervention group and from 4.9% to 4.3% for the control group.[14]

The aim of the present study was to compare recommendations for insulin pump settings made by different physicians treating patients with diabetes, in order to evaluate the extent of consistency among them. In addition, we compared the physicians' recommendations to those given by the automated software, the Advisor Pro.

2 MATERIALS AND METHODS

This was a multicentre, multinational non-interventional survey study. The study protocol was approved by the Rabin institutional review board (No. 000917).

We used the CareLink Pro Ver 4.0A (4.0.2504.1) diabetes data management (Medtronic Diabetes, Northridge, California) uploads of 15 patients, including CGM, self-monitoring of blood glucose and insulin pump data for 3 weeks, from the Institute for Endocrinology and Diabetes at Schneider Children's Medical Centre. Each physician received an anonymized dataset in a PDF file, as well as general de-identified information about the patient, including gender, age, HbA1c level, weight, height and body mass index. Physicians received details about the current pump settings of each patient (ie, basal rate plan, CR plan, CF plan, glucose targets and active insulin time). Each physician was asked to provide her/his proposed recommended changes to insulin pump settings and asked to state if any behavioural or lifestyle changes were recommended. All recommendations were provided in a uniform format on specialized forms given to each physician. An example of the form is provided in Appendix S2.

The cohort of physicians who participated in the study included nine consultants from three centres (in Israel, Slovenia and Germany) and 17 out of 30 physicians who participated in the European Society for Paediatric Endocrinology Diabetes, Obesity and Metabolism School held in April 2017 in Rome, Italy.

2.1 Data analysis

To compare the different recommendations of the physicians, the recommended daily adjustments were divided into 24 hourly periods (1 hour each) for basal, CR and CF plans, resulting in a total of 1080 comparison points (24 hours, 15 patients, three plans).

The physicians' recommendation points were compared for the relative changes to the patient's current pump settings in the basal, CR and CF plans between the physicians, between and within centres and between the physicians and the automated Advisor Pro algorithm.

The primary endpoints of the study were the percentage of comparison points in which there was full agreement on the trend of insulin dose adjustment (increase, decrease or no change) and full disagreement (opposite directions of insulin dose adjustments). Secondary endpoints were the percentage of comparison points that were in partial disagreement, divided into two categories, partial positive disagreement (increase insulin dose vs no change) and partial negative disagreement (decrease insulin dose vs no change).

Additional comparisons in pump setting adjustments were performed, comparing recommendations given by physicians based at the same centre, or given by faculty physicians vs fellow physicians, or given by physicians who practise in centres with high rates of pump use (>50%) vs those with lower pump use rates (Appendix S1).

2.2 Statistical analysis

A one-tailed, non-inferiority *t* test was used to assess whether the agreement (right tail) and the disagreement (left tail) between physicians and the Advisor Pro (26 pairs and total of 28 080 comparison points) was not inferior to the agreement and disagreement between pairs of physicians (351 pairs and total of 379 080 comparison points). The non-inferiority margin for the agreement *t* test was set as the 25th percentile of the distribution of the level of agreement between one physician and his/her colleague (351 pairs and total of 379 080 comparison points) per parameter. The non-inferiority margin for the disagreement *t* test was set as the 75th percentile of the distribution of the level of disagreement between one physician and his/her colleague (351 pairs and total of 379 080 comparison points) per parameter. The null hypothesis was that there is a difference in agreement/disagreement between physicians and the Advisor Pro, therefore, any significant *P* value ($P<0.05$) indicated that there was no significant difference between the physicians and Advisor Pro recommendations, indicating non-inferiority of the Advisor Pro. The number of similar or dissimilar time periods for each parameter basal, CR and CF change from the original programme, were compared among physicians and the Advisor Pro using general linear model repeated-measures

analysis with pairwise comparisons. The number of parameters that were changed for the same period of time among physicians and the Advisor Pro were compared using Pearson's χ^2 tests. The magnitude of the insulin dose adjustment between physicians and the Advisor Pro for the three variables (basal, CR and CF) was compared using a one-tailed, non-inferiority *t* test. The null hypothesis was that the magnitude of the difference in dose adjustments between physicians and the Advisor Pro was greater than the magnitude of the difference in dose adjustments between each pair of physicians, therefore, any significant *P* value ($P < 0.05$) indicated non-inferiority of the difference between physicians and the Advisor Pro in magnitude of insulin dose adjustments. The non-inferiority margin was the 75th percentile of the mean absolute difference.

3 RESULTS

A total of 25 paediatric physicians and 1 adult physician participated in the present survey study: 20 physicians from Europe (eight from Italy, four from Slovenia, three from Germany, three from the UK, 1 from Croatia and 1 from Poland), five physicians from Israel and one physician from Brazil. All participating physicians were active providers of diabetes patient care and were affiliated with 16 different centres that are experienced with insulin pump adjustments. The levels of experience of the physicians and their institutions, and the characteristics of the 26 participating physicians are presented in Table S1 in Appendix S1.

The characteristics of the patients whose data were used for the present survey are presented in Table S2 in Appendix S1. The downloads included data from 10 paediatric patients and five young adults (mean age 16.2 ± 4.3 years, six female, mean HbA1c 8.3 ± 0.9% [66.8 ± 7.3 mmol/mol]). All physicians completed the 15 forms of patients' pump recommendations, giving a total of 390 forms.

3.1 Degree of agreement in treatment adjustments

The proportion of full agreement between physicians on the direction of insulin adjustments of the basal, CR and CF settings was quite low and similar across the three assessed settings, within the range of 41% to 46% (Table 1). The similarity to the recommendations of the algorithm was significant, and full agreement was also within approximately the same range, at 41% to 48% ($P < 0.01$ for all three parameters; Figure 1A). The proportion of complete disagreement was notably lower than the proportion of full agreement and did not differ much between the parameters (range 9.5%-12%). Complete disagreement with the software tended to be lower than that between physicians for the CF plan (3.5%, $P = 0.03$), and similar for the two other plans, within a range of 8.5%-10% ($P < 0.01$ for both; Figure 1B).

Table 1. Results of comparisons for primary and secondary endpoints

	Among physicians	**Between Advisor Pro and physicians**	**P**
Primary endpoints (complete agreement)			
Agreement on basal change direction, %	41 ± 9	41.5 ± 8	<0.01
Agreement on CR change direction, %	45 ± 11	48 ± 11	<0.01
Agreement on CF change direction, %	45.5 ± 13	43.5 ± 11	<0.01
Disagreement on basal change direction, %	12 ± 7	10 ± 6	<0.01
Disagreement on CR change direction, %	9.5 ± 7	3.5 ± 2	<0.01
Disagreement on CF change direction, %	10 ± 8	8.5 ± 5	0.03
Secondary endpoints (partial agreement)			
One recommendation to increase/decrease basal insulin dose vs no change, %	47 ± 8	48.5 ± 6	<0.01
One recommendation to increase/decrease CR insulin dose vs no change, %	45.5 ± 12	48.5 ± 10	<0.01
One recommendation to increase/decrease CF insulin dose vs no change, %	45 ± 12	48 ± 9	<0.01

Abbreviations: CF, correction factor; CR, carbohydrate to insulin ratio.

Values are mean ± SD.

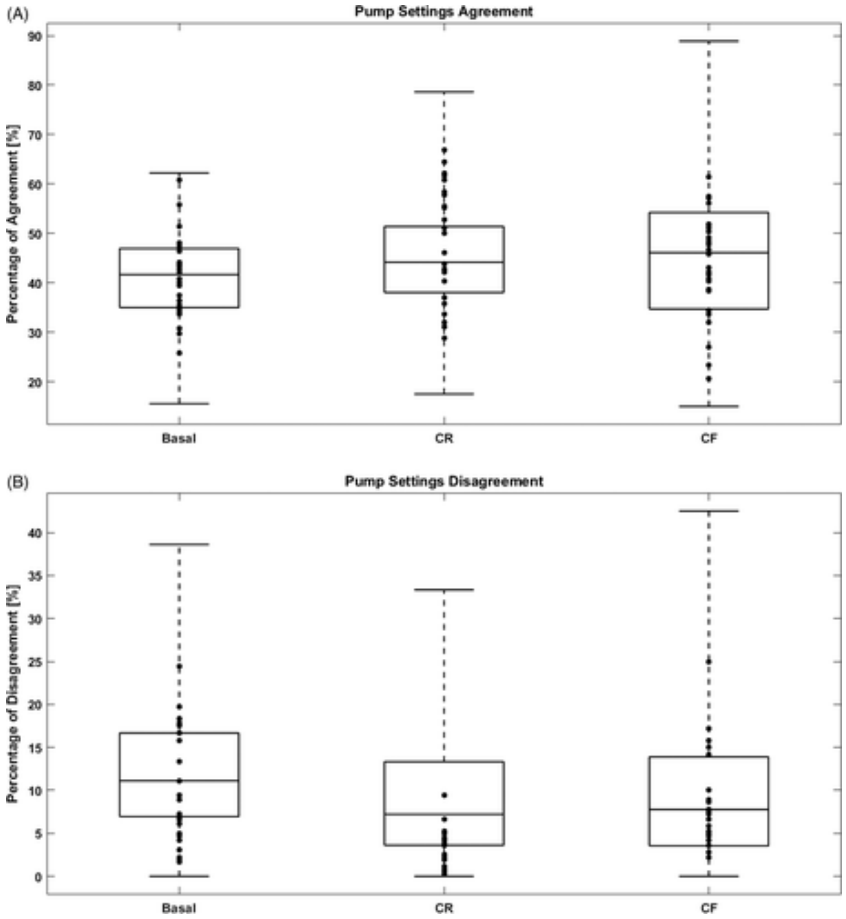

Figure 1. Primary endpoints: Level of complete agreement/disagreement. A, Level of agreement. B, Level of disagreement per pump settings. Box plot represents the physician-physician comparisons showing the median, interquartile range, minimum and maximum (n = 351) per pump setting feature. Dots represents the Advisor Pro-physician comparisons (n = 26) per pump setting feature. A non-significant difference was found between the level of agreement/disagreement among physicians and between physicians and the Advisor Pro (A: $P < 0.01$ all parameters, B: $P < 0.01$ for basal and carbohydrate to insulin ratio [CR] parameters and 0.03 for the correction factor [CF])

The proportions of partial agreement (to increase/decrease insulin dose vs no change) between physicians were similar to those observed for full agreement, and similar across recommendations (within the range of 45%-47%; Table 1). A significant similarity was found with the recommendations of the algorithm, and the proportion of partial agreement was ~48% across recommendations (Table 1).

Physicians working within the same centre were not found to provide similar recommendations. The level of agreement between physicians was 51.7%, 47.8% and 50.8% for sites 1, 2 and 3, respectively. The disagreement level was 4.2%, 4.7% and 9.2% for sites 1, 2 and 3, respectively. A significant difference (P = 0.018) in the distribution of the level of agreement/partial agreement/disagreement was found among the three different centres (Figure S1 in Appendix S1).

The level of centre experience with insulin pump use had no effect on degree of agreement; the results were similar between physicians in centres in which <50% patients were using insulin pumps (*n* = 12) and those in which >50% of the patients were using insulin pump therapy (*n* = 14). The seniority of physicians did not affect the agreement either. Similar results were also found between faculty physicians (*n* = 13) and fellows (*n* = 13; Table S3 in Appendix S1).

3.2 Magnitude of treatment adjustments

Figure 2 presents the median magnitude of change and the interquartile range of the increase and decrease in insulin dose adjustments for each of the three insulin-pump setting parameters. On average, in the cases in which physicians were in full agreement about the recommended direction of change, they tended to recommend small adjustments in the basal setting and an adjustment of ~20%-30% in CR and CF. A significantly similar magnitude of change was found between the Advisor Pro and the physicians' recommendations for the 3 variables: basal (P = 0.002), CR (<0.001) and CF (<0.001). The overall range from the minimal to the maximal recommended changes between the different physicians in the magnitude of recommended change was 94% larger than between the physicians and the Advisor Pro.

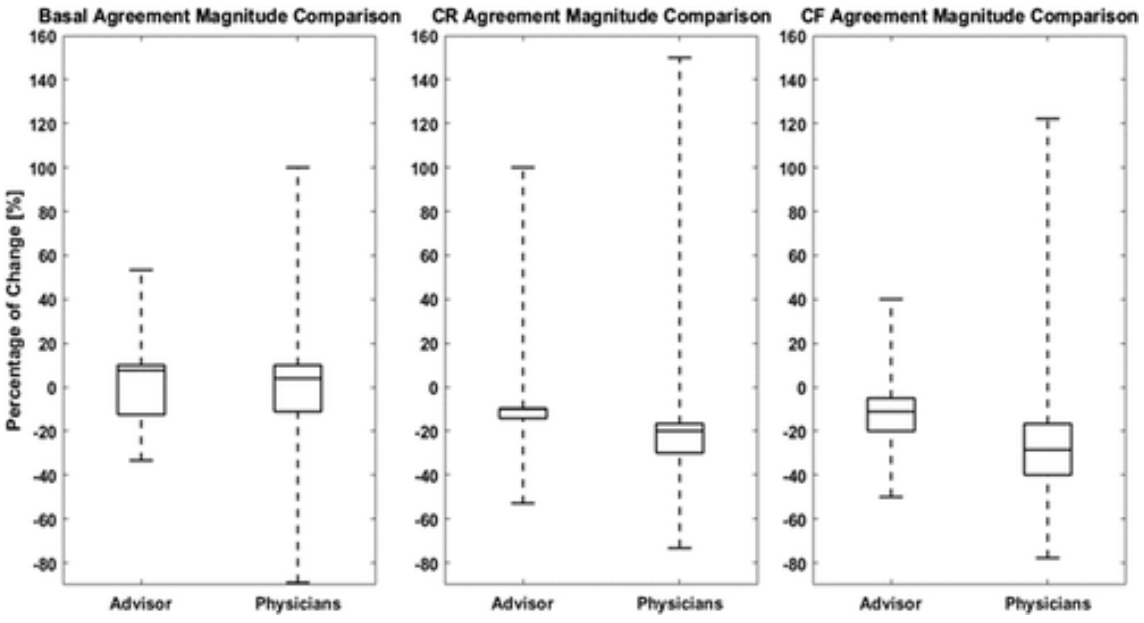

Figure 2. Magnitude of insulin pump dosing adjustments in cases of full agreement for basal, carbohydrate to insulin ratio (CR) and correction factor (CF) plans. Box plot represents the median, interquartile range, minimum and maximum (*n* = 351) per pump settings feature. The non-inferiority margin was 75th percentile of the mean absolute difference. A non-significant difference was found in the magnitude of change in cases of full agreement among physicians and between physicians and the Advisor Pro (P = 0.002 for basal and P < 0.01 for the CR and CF)

The magnitude of the relative dose adjustments (as a percentage) in cases of agreement in the direction of dose adjustment (increase or decrease) was found to be non-inferior between physicians and the Advisor Pro during the day as well as during the night (Table S4in Appendix S1); therefore, according to the null hypothesis, the magnitude of change of the Advisor Pro was at least equal to or less than the advised magnitude of change proposed by the physicians.

3.3 Number of time periods and insulin dosing parameter adjustments

Physicians tended to increase the number of basal periods: mean ± SD from 4.4 ± 1.5 to 4.9 ± 0.6 ($P = 0.11$) vs 7.7 ± 1.9 for the Advisor Pro ($P < 0.001$). The number of CR plan periods were changed by the physicians from 2.7 ± 1.4 to 3.2 ± 0.6 ($P = 0.07$) compared with 3.9 ± 1.3 for the Advisor Pro ($P < 0.01$). The number of CF plan periods were significantly changed by the physicians from 1.9 ± 1 to 2.3 ± 0.5 ($P = 0.012$) compared with 3.5 ± 1.1 for the Advisor Pro ($P < 0.01$; Table 2).

Table 2. Number of basal, carbohydrate to insulin ratio and correction factor rate periods of time

Insulin pump setting	Mean (SD) number of time periods			P
	Original	Physicians	Advisor Pro	
Basal	4.4 (1.5)[a]	4.9 (0.6)[a]	7.7 (1.7)[b]	<0.001
CR	2.7 (1.4)[a]	3.2 (0.6)[a]	3.9 (1.3)[b]	0.001
CF	1.9 (1)[a]	2.3 (0.5)[b]	3.5 (1.1)[c]	0.001

Rates with different superscripts (a, b, c) differ significantly from each other in that row at P< 0.05 (adjustment for multiple comparisons: least significant difference). Abbreviations: CF, correction factor; CR, carbohydrate to insulin ratio.

General linear model, repeated measures with analysis of pairwise comparisons.

In instances where there was a decision to change insulin dose, physicians tended to change one, two or three variables (basal, CR or CF) at the same period of time in 28.5%, 33.5% and 23%, compared with 24.5%, 27% and 16.5% of cases, respectively, for the Advisor Pro ($P < 0.001$).

4 DISCUSSION

Substantial diversity was found among different physicians in insulin dose recommendations made for pump settings based on CGM data. The overall level of agreement in the direction of insulin dose adjustment was only ~45% for each of the pump variables (basal, CR and CF). This level of agreement did not differ, even when physicians were based in the same centre or among centres with high frequency of pump use. The automated advice given by the Advisor Pro did not differ significantly from the advice given by the physicians in the direction and magnitude of the insulin dosing.

Physicians within the same centre were also found to agree only on approximately half of the recommended changes; thus, even in centres with experience in diabetes technology, incorporating multidisciplinary teams, educational models and defined glucose target goals, there was a diversity in decision-making regarding insulin dose adjustments. An even more interesting finding was the level of complete disagreement, as some physicians wanted to increase the insulin dose at a point where others suggested reducing the dose. The level of disagreement was found to be somewhat higher for the basal decisions than for the CR and CF decisions. Among centres that were studied, the level of complete disagreement differed significantly and reached as high as >10% of overall decisions at one site.

The physicians as well as the Advisor Pro tended to advise an increase in the overall dose of insulin, more by modification of the CR and CF doses than by modification of the basal insulin doses; thus, more insulin may be given as boluses and less as basal doses. The finding that more insulin should be delivered as boluses than as basal doses has been observed in pump[15] and closed-loop[16] studies and was found to be associated with better glycaemic control and HbA1c levels.

The Advisor Pro recommendations were more conservative with respect to magnitude of change in insulin dosing because of the safety limits of the system. The median and interquartile range percentage of change for each variable (basal, CR and CF) was similar between the Advisor Pro and physicians. Nevertheless, some physicians recommended changes of a larger magnitude in both directions as high as 150% increase in insulin dosing. The percentage of change in dose recommendations of the Advisor Pro did not exceed beyond that of the physicians. The Advisor Pro adjusted the pump settings in small steps because of its inherent safety measures. The magnitude of change is more permissive in cases of hypoglycaemia, as fewer events are needed to reduce the amount of insulin dose as compared to hyperglycaemic events. A recently published study showed that magnitude of dose changes by the physicians for 20 simulated patients on multiple daily injections and self-monitoring of blood glucose were greater than by dedicated algorithms.[17] This result points out the greater variability and challenges associated with managing patients on pumps using CGM.

Data in the literature are scarce regarding differences between different prescribers in the amount of insulin dose adjustments. A study from the Netherlands evaluated factors that influenced the decision

of 190 care providers in basal insulin titration for patients with type 2 diabetes. Even for type 2 diabetes, for which guidelines and official recommendations exist and adjustments are easier because only basal insulin is adjusted, insulin titration magnitude was found to be significantly different between providers.18

Physicians tended to increase the number of periods of each pump setting parameter from the baseline settings; however, statistical significance was reached only for the CF. The Advisor Pro recommended adjustments for significantly more basal rates than did the physicians and to a lesser extent, for the CR and CF rates. The Advisor Pro uses a unique algorithm that estimates the insulin requirements and was therefore able to recommend significantly more time periods. Studies have shown the need for different insulin requirements throughout the day, which depend mainly on age and on the stage of puberty.19, 20 Insulin pump therapy can provide a basal delivery of insulin in a more physiological way and can mimic the circadian needs. A euglycaemic clamp study showed that it takes 2.5 to 4 hours until a considerable change in basal infusion leads to a new steady-state level,21 therefore, up to 10 basal rates are effective with current insulin analogues.

Another difference was found for the number of parameters that were simultaneously adjusted to increase the insulin dose within the same time frame. Physicians tend to change insulin dosing in more than one variable in the same time frame more often than the Advisor Pro.

There were cases that physicians agreed upon more than others. For example, in one case, 92% of physicians suggested a decrease in the CF. In this particular case, the patient had several correction boluses which did not result in blood glucose-lowering. The Advisor Pro provided the same recommendation.

Dosing recommendation is one of the main tasks patients and healthcare providers deal with daily in diabetes management. Insulin dose adjustments are needed22, 23 and the newly available devices and the data they generate may help facilitate this process. Nevertheless, even with the recent availability of unified diabetes management platforms, this task remains challenging24. People with type 1 diabetes, their caregivers and their healthcare providers are often overwhelmed by the information collected via these platforms. The ability to transform this amount of data into actionable knowledge, which could be used to adjust therapies and better manage daily activities, is still lacking. Additionally, the number of people with diabetes is rising worldwide, but the number of diabetes specialists has not kept pace with this increasing prevalence.25-27 The low frequency of patient-physician interactions (just once every 3-4 months) and the fact that insulin profile optimization is very time-consuming, even for experts, raise the need for a tool that can transform data into insulin therapy adjustments between clinic visits. The study made comparisons between physicians and automated dose adjustments based on digital data alone and not those given by care providers during face-to-face visits with patient input. The percentage of agreement between the automated system and the physicians might have been different if we had incorporated patients' input regarding exercise, stress, alcohol intake and so on. The lack of patient input will be addressed by using the next-generation advisors that may incorporate data gathered from the digital ecosystem (internet of things).

A few small-scale studies have shown that insulin dose adjustments made by software for patients using multiple daily injections and self-monitoring of blood glucose can be made safely and efficiently. The recommendations were found to be similar to what the caregivers would advise[28, 29] and may reduce the need for additional clinic visits for patients with type 2 diabetes.[30] The present study supports the notion that an automated decision support system that can give automated advice on changing insulin pump settings provides similar recommendations to those given by experienced physicians, making it akin to another member in the healthcare team. In the future, this tool can be used to achieve better self-management by giving its recommendations directly to the patients. In addition, as closed-loop systems will become more available mainly for those who use pump and CGM, the main role of the Advisor Pro will be its use for those who are treated with an insulin pump and use self-monitoring of blood glucose.

The study is limited by the fact that it may not be possible to extrapolate the findings to other groups of physicians or prescribers, such as primary healthcare providers, nurses or diabetes educators. Our study population included adolescents and young adults and did not consider individual targets. That may have limited our ability to generalize the data to a broader population of people with type 1 diabetes. Although the Advisor Pro should not act differently in other groups of patients, the magnitude of change may vary. We may have found even larger differences among physicians as well as between physicians and the Advisor Pro if these variables had been included as insulin dosing and requirements do vary with age. The effectiveness of the insulin dosing adjustments was not evaluated in the present study because the aim was to determine whether there was agreement on pump adjustments among experienced physicians. The effectiveness of the automated system was tested in a small feasibility study that showed similarity in outcomes between recommendations given by physicians and those given by the Advisor Pro.[14] The algorithm effectiveness is being tested in a non-inferiority, multicentre, multinational, parallel-design study including 112 patients to evaluate the system's decisions compared to those made by physicians (ClinicalTrials.gov identifier: NCT03003806).

The advantage of the present study was the number of physicians that participated in the survey from different centres, which enabled us to compare, for the first time, human and automated decisions in insulin pump setting adjustments.

In conclusion, this survey showed that there was a wide variability in the ways experienced physicians chose to adjust insulin pump dosing and that automated adjustments did not differ from those given by different physicians in the direction and magnitude of insulin dosing. Future research assessing the clinical effects of recommendation strategies could serve as a basis for informed guidelines. Automated recommendations could serve as a tool for healthcare providers to make clinic visits more effective and to help adjust insulin dosing in-between visits.

ACKNOWLEDGMENTS

The authors wish to thank the following colleagues for assistance in the study: Shiri Diskin, PhD, for her assistance in editing this manuscript and Prof. David Steinberg of Tel Aviv University for assistance in the statistical analysis. Part of this work was presented at the 11th International Conference on Advanced Technologies & Treatments for Diabetes, Vienna, Austria February 14-17, 2018.

Conflict of interest

R.N. received honoraria for participation on the speaker's bureau of Novo Nordisk, Pfizer, Eli Lilly and Sanofi. R.N. owns DreaMed stock. R.N. reports two patent applications. E.D has received consulting fees from Animas, Insulet, Eli Lily and Company, has received research support from Dexcom, Animas, Insulet, Roche, Tandem, Lifescan and Xeris, and receives royalty payments on intellectual property related to closed-loop algorithms. T.S., I.M. are employees of DreaMed Diabetes. I.M. owns DreaMed stocks. N.B. received honoraria for participation on the speaker's bureau of Medtronic and Roche. N.B. owns DreaMed stock. O.K. has received honoraria for sitting on the advisory board of Novo Nordisk, and speaker's honoraria from Eli Lilly and Sanofi. O.K. owns DreaMed stocks. T. Biester has received honoraria for participation in the speaker's bureau of Medtronic, DexCom, YpsoMed, travel support from NovoNordisk, DexCom, AstraTeneca, and sitting on the DexCom Advisory Board. R.B, D.K, A.T, A.B, M.S, S.D.S, M.N.S, C.P, I.R, D.T, C.B, S.C, A.R, B.P, D.G, R.S, Iv.R, P.B, J.S.O, C.S, G.B and M.Y.G have no conflict of interest related to this study. T. Battelino served on the advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, DreaMed Diabetes and Bayer Health Care. T. Battelino's institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. T. Battelino received honoraria for participating on the speaker's bureau of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. T. Battelino owns DreaMed stock. T.D has received research support/consulting fees from Abbott Diabetes Care Inc., AstraZeneca, Novo Nordisk A/S, Eli Lilly and Company, Boehringer Ingelheim GmbH, BD Medical-Diabetes Care, Lexicon, Medtronic MiniMed, Inc., Lexicon Pharmaceuticals, Inc., Roche Diagnostics, Sanofi-Aventis Deutschland GmbH, Johnson & Johnson. T.D. owns DreaMed stock. E.A is employee of DreaMed Diabetes. E.A owns DreaMed stock. M.P. is a member of the Advisory Board of AstraZeneca, Sanofi, Animas, Medtronic, Bayer Health Care and Board Member of C.G.M.3 Ltd., Consultant of Bristol-Myers Squibb, D-medical, Ferring Pharmaceuticals, Andromeda Biotech. The Institute headed by M.P. received research support from Medtronic, Novo Nordisk, Abbott Diabetes Care, Eli Lilly, Roche, Dexcom, Sanofi, Insulet Corporation, Animas, Andromeda, and Macrogenics. M.P. has been paid lecture fees by Sanofi, Novo

Nordisk, Roche, and Pfizer. He is a stock/shareholder of C.G.M.3 Ltd. and DreamMed Diabetes. M.P. reports two patent applications.

Author contributions

R.N., E.A., M.P. contributed to the study concept and design, collected data, participated in data analysis and interpretation, and drafted, reviewed, and edited the manuscript. E.D. contributed to the study concept and design, participated in data analysis and interpretation, reviewed and edited the manuscript. T.S. collected data, participated in data analysis and interpretation, and drafted, reviewed and edited the manuscript. N.B., O.K., R.B, T. Biester, D.K., A.T, B.A., T. Battelino, T.D., M.S, S.D.S, M.N.S, C.P, I.R, D.T, C.B, S.C, A.R, B.P, D.G, R.S, Iv.R, P.B, J.S.O, C.S. and G.B participated in the study survey, and reviewed and edited the manuscript. I.M. collected data, participated in data analysis and interpretation, and reviewed and edited the manuscript. Y.G.M participated in data analysis and interpretation, statistical analysis, and reviewed and edited the manuscript.

SUPPORTING INFORMATION Additional supporting information may be found online in the Supporting Information section at the end of the article

REFERENCES

1. American Diabetes Association 6. Glycemic targets: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.
2. Heinemann L, Fleming GA, Petrie JR, Holl RW, Bergenstal RM, Peters AL. Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting and research needs. A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. Diabetologia. 2015;58(5):862-870.
3. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. Diabetes Care. 2015;38(6):971-978.
4. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med. 2015;32(8):1036-1050.
5. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. Pediatrics. 2006;117(6):2126-2131.
6. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008;25(7):765-774.
7. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy With severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA. 2017;318(14):1358-1366.
8. Shalitin S, Ben-Ari T, Yackobovitch-Gavan M, et al. Using the Internet-based upload blood glucose monitoring and therapy management system in patients with type 1 diabetes. Acta Diabetol. 2014;51(2):247-256.
9. Pettus J, Edelman SV. Recommendations for using real-time continuous glucose monitoring (rtCGM) data for insulin adjustments in type 1 diabetes. J Diabetes Sci Technol. 2017;11(1):138-147.
10. Aleppo G, Laffel LM, Ahmann AJ, et al. A practical approach to using trend arrows on the dexcom G5 CGM system for the management of adults with diabetes. J Endocr Soc. 2017;1(12):1445-1460.
11. Prahalad P, Tanenbaum M, Hood K, Maahs DM. Diabetes technology: improving care, improving patient-reported outcomes and preventing complications in young people with Type 1 diabetes. Diabet Med. 2018;35(4):419-429.
12. Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. J Diabetes Sci Technol. 2017;11(5):1015-1027.
13. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes? A systematic review, meta-analysis, and GRADE of 14 randomized trials. Diabetes Care. 2016;39(11):2089-2095.
14. Eran A. Advisor is getting results. In: ATTD 2018 - 11th International conference on Advanced Technologies & Treatments for Diabetes, Vienna, Austria; 2018. February 14-17, 2018.
15. Danne T, Battelino T, Jarosz-Chobot P, et al. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. Diabetologia. 2008;51(9):1594-1601.

16. Nimri R, Muller I, Atlas E, et al. MD-logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care. 2014;37(11):3025-3032.

17. Davidson MB, Duran P, Davidson SJ, Lee M. Comparison of insulin dose adjustments by primary care physicians and endocrinologists. Clin Diabetes. 2018;36(1):39-43.

18. Simon AC, Schopman JE, Hoekstra JB, et al. Factors that drive insulin-dosing decisions of diabetes care providers: a vignette-based study in the Netherlands. Diabet Med. 2015;32(1):69-77.

19. Bachran R, Beyer P, Klinkert C, et al. Basal rates and circadian profiles in continuous subcutaneous insulin infusion (CSII) differ for preschool children, prepubertal children, adolescents and young adults. Pediatr Diabetes. 2012;13(1):1-5.

20. Danne T, Battelino T, Kordonouri O, et al. A cross-sectional international survey of continuous subcutaneous insulin infusion in 377 children and adolescents with type 1 diabetes mellitus from 10 countries. Pediatr Diabetes. 2005;6(4):193-198.

21. Heinemann L, Nosek L, Kapitza C, Schweitzer MA, Krinelke L. Changes in basal insulin infusion rates with subcutaneous insulin infusion: time until a change in metabolic effect is induced in patients with type1 diabetes. Diabetes Care. 2009;32(8):1437-1439.

22. Davidson MB. How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. Diabetes Care. 2009;32(2):370-372.

23. Kaufman FR, Halvorson M, Carpenter S. Association between diabetes control and visits to a multidisciplinary pediatric diabetes clinic. Pediatrics. 1999;103(5 Pt 1):948-951.

24. Borot S, Benhamou PY, Atlan C, et al. Practical implementation, education and interpretation guidelines for continuous glucose monitoring: a French position statement. Diabetes Metab. 2018; 44(1):61-72.

25. Vigersky RA, Fish L, Hogan P, et al. The clinical endocrinology workforce: current status and future projections of supply and demand. J Clin Endocrinol Metab. 2014;99(9):3112-3121.

26. Association of American Medical Colleges. The complexities of physician supply and demand 2017 Update: Projections from 2015 to 2030. https://aamc-black.global.ssl.fastly.net/production/media/□ler_public/a5/c3/a5c3d565-14ec-48fb-974b-99fafaeecb00/aamc_projections_update_2017.pdf

27. IDF. Diabetes atlas - 2017. www.diabetesatlas.org/resources/2017-atlas.html. Accessed December 4, 2017.

28. Bashan E, Hodish I. Frequent insulin dosage adjustments based on glucose readings alone are sufficient for a safe and effective therapy. J Diabetes Complications. 2012;26(3):230-236.

29. Bergenstal RM, Bashan E, McShane M, Johnson M, Hodish I. Can a tool that automates insulin titration be a key to diabetes management? Diabetes Technol Ther. 2012;14(8):675-682.

30. Bajaj HS, Venn K, Ye C, Aronson R. Randomized trial of long-acting insulin glargine titration web tool (LTHome) versus enhanced usual therapy of glargine titration (INNOVATE Trial). Diabetes Technol Ther. 2016;18(10):610-615.