Journal of Diabetes and Its Complications 26 (2012) 230–236

Contents lists available at SciVerse ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Frequent insulin dosage adjustments based on glucose readings alone are sufficient for a safe and effective therapy ☆

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ARTICLE INFO

Article history:
Received 4 December 2011
Received in revised form 10 March 2012
Accepted 13 March 2012
Available online 20 April 2012

Keywords:
Insulin therapy
Dosage adjustments
A1C

ABSTRACT

Problem: Frequent dosage adjustments are necessary to achieve effective insulin therapy. However, a controversy surrounds the pertinent clinical parameters required to make effective and safe insulin titrations. We hypothesize that glucose readings are sufficient to adjust insulin dosage provided that it is done on a weekly basis.

Methods: In a prospective pilot study, we recruited 14 subjects with suboptimally controlled insulin-treated Type-2 and Type-1 diabetes. Subjects were treated with basal-bolus insulin therapy that was titrated weekly for 12 weeks. Dosage adjustments were made by the study Endocrinologist by reviewing subjects' glucose readings, exclusively based on logsheets and contingent upon the approval of the on-site study team. To corroborate that the glucose readings were sufficient for making dosage adjustments, we used software to process only glucose readings and recommend insulin dosage adjustments. The recommendations made by the software were retrospectively compared to the ones made by the study Endocrinologist.

Results: All $N=568$ recommendations were approved by the study team and in 99.3% of the cases the recommendations were clinically similar to the ones made by the software. No hazardous disagreements were found. The mean A1C improved from 9.8% (±2.0) to 7.9% (±1.3) ($p=0.001$) in 12 weeks and the weekly mean glucose progressively improved from 220.3 mg/dl (±51.9) to 151.5 mg/dl (±19.2) ($p<0.0001$). The frequency of minor hypoglycemia was 22.7 per patient-year in subjects with Type-2 diabetes and 42.7 in the subjects with Type-1 diabetes. No severe hypoglycemic events occurred.

Conclusions: Glucose readings are sufficient to adjust insulin therapy in a safe and effective manner, when adjustments are made on a weekly basis. Thus, dedicated software may help adjust insulin dosage between clinic visits.

Published by Elsevier Inc.

1. Introduction

Insulin is the earliest and one of the most widely-used drugs for diabetes treatment, yet ambiguity still surrounds its unsatisfactory therapeutic success-rate (referred to here as the "insulin paradox"). Although insulin belongs to an exclusive group of medications that do not have an upper dosage limitation, two-thirds of insulin users do not achieve the therapy goal (A1C<7%), and become susceptible to diabetes complications (Hoerger et al., 2008; Koro et al., 2004). It has been hypothesized that lack of patients' compliance, lack of motivation, drug limitations, and under-use of carbohydrate counting were the causes for the low success rate. Yet, it has been demonstrated that:

- Patients' compliance to insulin therapy is generally sufficient (Cramer et al., 2008; Spoelstra et al., 2003);
- Insulin-treated patients managed in extended clinical trials can be highly successful in achieving the A1C goal for years (2002; Holman et al., 2009);
- Regimens using fixed doses of basal or premixed insulins can be highly effective (Buse, Wolffenbuttel et al., 2009; Holman et al., 2009)
- Patients with Type-2 diabetes treated with basal-bolus therapy can attain good glycemic control without carbohydrate counting (Bergenstal et al., 2008);
- And superior control achieved and maintained during prolonged studies like the DCCT vanishes shortly after the study, when patients are referred back to their original clinics (2002).

The "insulin paradox" ensues from a discrepancy between the dynamic nature of the therapy and the low frequency of dosage

☆ Author Disclosure Statement: Both Israel Hodish and Eran Bashan are affiliated with Hygieia INC. a company developing medical devices based on the described software. The PI and the study team in New-Jersey are not affiliates of Hygieia and did not participate in the preparation of the manuscript.

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1056-8727/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.jdiacomp.2012.03.012

adjustments (Davidson 2009). While insulin dosage is adjusted during sporadic clinic visits (typically every 3–6 months), insulin requirements change repeatedly over time as evidenced by the rapid changes in average weekly glucose between clinic appointments (Bashan et al., 2011). Conversely, in clinical studies when insulin dosage is adjusted every one to four weeks, regimens become effective in the majority of the cases (Bergenstal et al., 2008; Bretzel et al., 2008; Buse et al., 2009; Davies et al., 2007; Davidson and Lewis 2000, 2002; Herman et al., 2005; Holman et al., 2007; Kennedy et al., 2006; Oyer et al., 2009), compared to about a one-third success rate in traditional settings (Hoerger et al., 2008; Koro et al., 2004). Historically, (with clinical studies as an exception), the funding and manpower are not available to communicate with patients every few weeks to adjust insulin dosage. The growing mismatch between patients' needs and the limited availability of care providers trained in insulin management (Hayes et al., 2008), disallows extensive implementation of frequent insulin-dosage titrations. Therefore, we propose that alternative approaches be sought that empower patients to titrate their own insulin regimens as often as needed between clinic visits. To that end, it is necessary to thoroughly explore the process of frequently adjusted insulin therapy.

Many studies incorporating insulin titration protocols have published the guidelines used by the study team to provide dosage adjustments (Bergenstal et al., 2008; Buse et al., 2009; Davies et al., 2007; Holman et al., 2007; Kennedy et al., 2006). In all guidelines, glucose readings were the only parameter used to titrate insulin. It is unclear, and often questionable, however, how rigorously these guidelines were followed. We hypothesize that glucose readings, as a single parameter, are sufficient to adjust insulin dosage, provided that it is done on a weekly basis.

To test this hypothesis we previously published a retrospective analysis showing that glucose readings were the only parameter required by software to accurately recreate an expert-team dosage adjustment to basal-bolus insulin therapy in more than 2500 recommendations (Bashan et al., 2011). In the current article we provide prospective evidence supporting the hypothesis in 568 recommendations.

2. Methods

2.1. Study Design

This was a three-month open-label prospective study, including patients with insulin-treated Type-2 diabetes and Type-1 diabetes with inadequate glycemic control (The study is registered with ClinicalTrials.gov, number NCT01014832). It was conducted by TKL Research (Rochelle Park, NJ) after being reviewed and approved by Quorum Institutional Review Board (Seattle, WA), and all subjects provided written informed consent. The study team and the principal investigator (PI) were located in New-Jersey while the study Endocrinologist (Israel Hodish) was located in Michigan. Subjects were eligible to participate if they were 25 to 65 years of age of any ethnic background, having either insulin-treated Type-2 diabetes or Type-1 diabetes, and an A1C $\geq$ 7.6%. Patients with Type-1 diabetes were required to incorporate carbohydrate counting in their regimens and to use at least 25 units of insulin per day. Subjects were excluded from the trial if they had a history of more than two episodes of severe hypoglycemia in the past year (see definition below); had Hypoglycemia Unawareness; were having significant physical, psychological, or cognitive impairment; had severe cardiovascular disease; had severe anemia (hematocrit <25% in women or <30% in men); had significant renal disease (creatinine >2.0 mg/dl); had significant liver disease (cirrhosis or transaminases more than 3 times the upper limit); had a body mass index (BMI) >45 kg/m^2; or were pregnant or breastfeeding.

The study included three visits. During the first visit subjects reviewed and signed the informed consent form; and examined and provided basic data including medical history, recent glucose readings, and past year lab results. During that visit a blood test for A1C was collected (determined by the high pressure liquid chromatography method or HPLC). During the second visit, the study team determined eligibility. Subjects with Type-2 diabetes were to discontinue previous insulin regimens and other diabetes medications (except for Metformin), and were given a prescription for basal-bolus insulin therapy and an initial insulin dosage. To determine the initial dosage, first the total daily units were determined by reviewing previous dosage, recent glucose readings, and A1C. Approximately 50% of the total daily insulin was given as long-acting insulin (Insulin Glargine®; Sanofi-Aventis, Bridgewater, NJ) at bedtime, while the remaining 50% was evenly divided between meals as rapid-acting insulin (Lispro®; Eli Lilly, Indianapolis, IN or Aspart®; Novo-Nordisk, Princeton, NJ). Rapid-acting insulin was given as a basic meal dose for each meal, with a correction factor.

Subjects with Type-1 diabetes were asked to continue their short- and long-acting insulin formulations with the adjusted dosage. In addition to the total daily units, the rapid-acting insulin dosage (expressed as units to carbohydrate ratios plus a correction factor) was given for each meal. Before anticipated strenuous physical activity, all subjects were instructed to reduce the prandial rapid-acting insulin dose, preceding the activity, by 10% for each anticipated half-hour of activity and both symptoms and remedial approaches for hypoglycemia were reviewed.

All subjects were asked to monitor their capillary glucose level four times a day (before meals and at bedtime) as well as a weekly nocturnal reading. Subjects recorded glucose readings, time of measurements, insulin doses, and carbohydrate quantity (if applicable) in dedicated logsheets. Each week, the logsheets were sent to the study team by fax or email or were physically brought (copy) to the study center. Logsheets were faxed to the study Endocrinologist in Michigan who then adjusted insulin dosage based on the reported glucose readings. Within twenty-four hours, the new dosage recommendations were forwarded to the on-site PI for approval and then conveyed to the subjects over the phone. While the PI and the study team were in contact with the subjects, the study Endocrinologist did not have direct contact with the subjects and was only exposed to their weekly logsheets. After twelve weeks, the subjects returned to the study center and their final A1C was determined.

2.2. Determination of adherence

Therapy adherence served as a marker for quality control to corroborate the weight of the study Endocrinologist's instructions. For each patient, rapid-acting insulin doses during the sixth week were individually compared to the dosage instructions for this particular week. The deviation of each administered dose from the instruction was expressed as a percentage. For example, if a subject's glucose preceding lunch was 180 mg/dl and the subject was instructed to inject 24 units of Lispro based on his basic dose and correction factor but the subject actually injected 26 units, this dose would have registered as 108.3%.

2.3. Main study outcome

2.3.1. Study outcomes were

- The fraction of dosage adjustments made by the study Endocrinologist (based only on logsheets) that were approved by the on-site study-team.

- The distance between the adjustments made by the software (based only on glucose readings) to the approved recommendations made by the study Endocrinologist (see analysis below). The efficacy of dosage adjustments was assessed by attenuations in weekly mean

Table 1
Characteristics of the study population.

Subjects (*n*)	14
Age (years)	49.9±11.5
Sex (male)	8 (57.1)
Race	
Caucasian	10 (71.5)
Black	1 (7.1)
Hispanic	2 (14.3)
Native American	1 (7.1)
Type of diabetes	
Type-1	3 (21.4)
Type-2	11 (78.6)
Duration of diabetes (years)	17.4±10.9
History of diabetes complications	
Retinopathy	2
Nephropathy	0
Neuropathy	3
History of cardiovascular complications	
Hypertension	6 (42.8)
Dyslipidemia	10 (71.4)
Cigarette smoking (current)	5 (35.7)
Ischemic heart disease/Heart failure	4 (28.6)
BMI (kg/m^2)	34.3±4.8
Initial A1c (%)	9.8±2.0
Data are means±SD or n (%)	

glucose during the study and attenuations in A1C. The former was considered as a more dependable short-term marker for improved glycemia since longer time would have been required to achieve a new steady state of A1C (Koenig et al., 1976).

- The safety of dosage adjustments was assessed by the occurrence of hypoglycemia.

Minor hypoglycemia was defined as self-treated blood glucose level ≤65 mg/dl. Severe hypoglycemia was defined as ≤50 mg/dl, associated with neuroglycopenic symptoms that require assistance by another person.

2.4. Post-hoc analysis

To support the hypothesis, it was essential to exclude subliminal integration of other clinical parameters that could have been found in the logsheets and may have been used to adjust insulin dosage weekly. Therefore, the study team used software (Bashan et al., 2011) that adjusts insulin dosage based on time-tagged glucose readings that are blind to any additional clinical parameters. The new recommended dosage generated by the software was used for comparison with the original dosage provided to each patient by the study Endocrinologist. This software, developed in 2007 by Drs. Bashan and Hodish at the University of Michigan, was described in a another publication (Bashan et al., 2011).

2.5. Similarity metric (i.e. a tool to classify distance)

Differences between the study Endocrinologist's recommendations for weekly insulin dosage adjustments and the recommendations made by the software were classified into six categories, as previously published (Bashan et al., 2011):

1. Identical: the software and study Endocrinologist made the same dosage recommendation.
2. Within 10%: the dosage recommended by the software was within 10% of the dosage recommended by the study Endocrinologist. In addition, the two dosage modifications were in the same direction (i.e. the software did not recommend to increase the dosage while the study Endocrinologist recommended to decrease the dosage or vice versa).
3. Within 10%–20%: the dosage recommended by the software was within 10%–20% of the dosage recommended by the study Endocrinologist. In addition, the two dosage modifications were in the same direction.
4. Different; 10%–20%: The software recommended increasing the dosage by 10%–20% while the study Endocrinologist recommended decreasing the dosage.
5. Different; more than 20%: The software recommended increasing the dosage by more than 20% while the study Endocrinologist recommended decreasing the dosage.
6. Other: all other cases (not complying with categories one through five). This category included instances in which the software recommended decreasing the dosage while the study Endocrinologist recommended increasing the dosage. For illustration, if the study Endocrinologist recommended increasing a meal dosage from 20 units to 22 units and the software decreasing from 20 to 19, this difference would be classified as 'Other'.

Of the above, categories four and five were defined as "different" and represented potentially hazardous disagreement between the software and the study Endocrinologist.

We considered the software recommendations to be "clinically equivalent" to the study Endocrinologist recommendations if they were classified in category one, two, or three. We assumed that a 20% difference is a reasonable value that can be seen in routine clinical settings. Moreover, it has been shown that identical insulin injections can result in different plasma insulin profiles (can exceed 20%) due to the complex process of insulin absorption and dispersion (Heinemann, 2002). For illustration, we believe that it is not unreasonable in clinical settings to have one care provider increasing lunchtime Lispro from 20 units to 21 and another care provider from 20 units to 25, using data from the same patient. The difference between these two examples is almost 20%.

2.6. Statistical analysis

The process for recommending insulin dosage, by either the study team or the software, is not a random process. Therefore, we neither performed nor presented statistical comparisons between the software and study Endocrinologist's recommendations. Instead, the similarity metric was used to measure the distance between the two sets.

Normality was assessed by Shapiro–Wilk test. Attenuations in weekly mean glucose were assessed for statistical significance by the repeated-measurements-ANOVA test. Patients' A1C, were compared by paired two-tailed Student *t* test. Results are presented as mean ± standard-deviation (SD) and p-value <0.05 was defined as statistically significant.

3. Results

3.1. Study population

Fourteen patients were recruited (eleven with Type-2 diabetes and three with Type-1), and twelve completed the study follow-up. Two subjects (one with Type-2 diabetes and one with Type-1) were

Table 2
Diabetes medications before enrollment.

Basal-Bolus insulin therapy	10 (71.4)
Long-acting insulin alone	2 (14.4)
Premix/biphasic insulin	1 (7.1)
Other insulin	1 (7.1)
Metformin	4 (28.6)
Glipizide	1 (7.1)
Glimepiride	1 (7.1)
Rosiglitazone	1 (7.1)
Exenatide	2 (14.3)

Data are *n* (%).

not compliant with the study protocol and withdrew after eight and four weeks, respectively. Except for final A1C, data from the two patients who withdrew from the study were included in the analysis (their glucose readings and initial A1C). The entire study population was cumulatively followed for 3 patient-years. Subjects' disposition is described in Table 1.

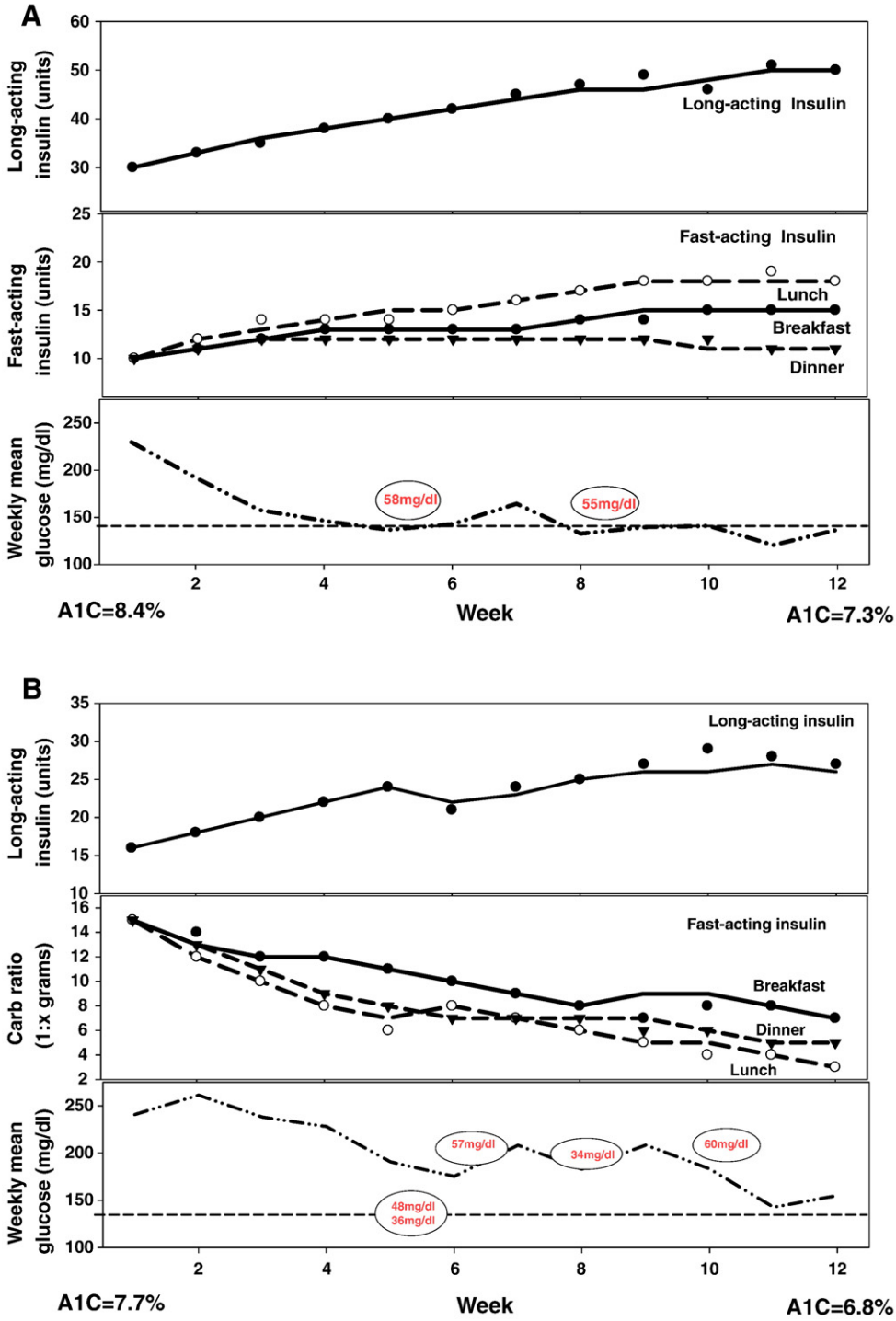

Fig. 1. Similarity between the dosage modifications made by the software and the study Endocrinologist. A) An example of a fifty-seven year old man with twenty year history of Type-2 diabetes. The graph depicts dosage adjustments for long-acting insulin in units, basic rapid-acting insulin meal doses for each meal in units, and weekly mean glucose in mg/dl. During these twelve weeks A1C improved from 8.4% to 7.3% in the expense of two episodes of minor hypoglycemia that occurred in weeks five and eight. Lines represent dosage recommendations made by the study Endocrinologist and markers represent adjustments recommended by the software. In each individual week, the difference between dosage adjustments made by the study Endocrinologist and the software is represented by the distance between the line and the marker, respectively. B) An example of a fifty-eight year old man with forty-five year history of Type-1 diabetes, having weekly episode of hypoglycemia before the study. The graph depicts dosage adjustments for long-acting insulin in units, with a denominator of rapid-acting insulin carbohydrate ratios in grams (e.g. one unit for every twelve grams of carbohydrates), and weekly mean glucose in mg/dl. During these twelve weeks A1C improved from 7.7% to 6.8% in the expense of five episodes of minor hypoglycemia. Lines represent dosage recommendations made by the study Endocrinologist and markers represent adjustments recommended by the software. C) Distance between recommendations made by the software and the study Endocrinologist. In more than 99% of the cases the software made dosage recommendations that were clinically similar to the ones made by the study Endocrinologist.

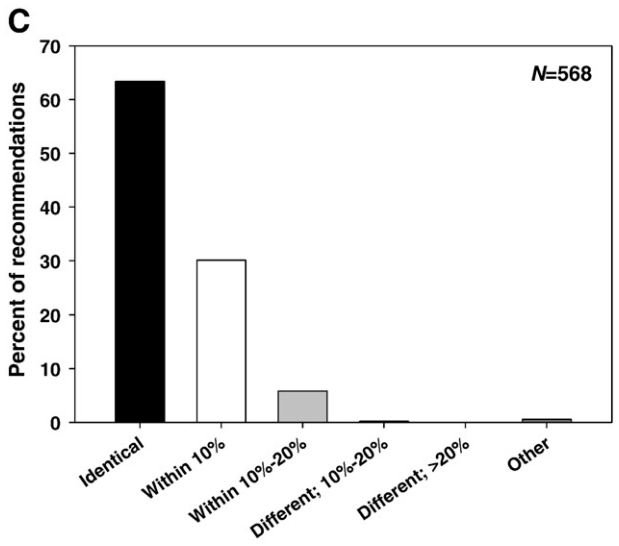

Fig. 1. (*continued*).

Ten subjects were treated with basal-bolus insulin therapy prior to the study, of whom three had Type-1 diabetes and seven had Type-2 (Table 2). Four subjects with Type-2 diabetes were treated with Metformin before and during the study. The mean total daily insulin dosage was 70.3 (±27.4) (0.63 units/kg) at the beginning of the study and 116.7 (±54.5) (1.1 units/kg) at study end.

3.2. Subjects' adherence

Subjects performed 25.9 (±1.9) glucose readings during the first week of the study and 25.8 (±3.6) during the last week ($p = 0.9$). Weekly glucose measurements ranged from 11 to 33, corresponding to 1.6 to 4.7 readings per day. During week six, 91.4% of the rapid-acting doses were administered as instructed and in 4.3% of the cases the rapid-acting doses deviated by less than 10% (about one event per patient-week) from the recommended dose. We assumed that in these rare cases, subjects deviated from the prescribed dose due to factors such as decreased food intake or increased physical activity.

3.3. A dedicated software, recreated the endocrinologist's recommendations using only glucose readings

A database of $N = 568$ recommendations for weekly insulin dosage adjustments (both for rapid-acting and long-acting insulin) was used for comparison. For each subject, recommendations were compared for the following categories: i) long-acting insulin; ii) rapid-acting insulin carbohydrate ratio (if applicable); iii) basic rapid-acting insulin meal doses (if applicable). An example for a subject with Type-2 diabetes is shown in Fig. 1A and an example for a subject with Type-1 diabetes is shown in Fig. 1B. All recommendations made by the study Endocrinologist (based on subjects' logsheets) were approved by the on-site study team.

In a post-hoc analysis, glucose readings and prior dosage for each week were used as the only input to the software, making it blind to any other clinical parameter. Fig. 1C shows that the software made "identical" (similarity metric category one) dosage recommendations in 63.4% ($n = 360$) of the cases, and that 30.1% ($n = 171$) were "within 10%" (category two), 5.8% ($n = 3$) were "within 10%–20%" (category three), and three cases were categorized as "other" (category six).

A single case was considered "different; 10%–20%" (category four) and resulted from data discrepancy due to a misread of a subject's handwriting in a single glucose-reading (94 mg/dl was read as 44 mg/dl). No cases of "different; greater than 20%" (category five) were noted.

In summary, 99.3% of the software recommendations (using only glucose measurements to adjust the prior dosage) yielded clinically equivalent insulin dosage adjustments to those of the study Endocrinologist

3.4. Weekly insulin dosage adjustments using glucose readings, resulted in superior glycemic control

The mean of the weekly glucose readings was 220.3 mg/dl (±51.9) at the beginning of the study and was 151.5 mg/dl (±19.2) at the end of the study ($p < 0.001$) (Fig. 2A). The mean A1C was 9.8% (±2.0) ($N = 14$) before enrollment (median 9.4%) and 7.9% (±1.3) ($N = 12$) following the twelve weeks of weekly adjusted basal-bolus insulin therapy (median 7.7%); $p = 0.001$. The mean improvement of A1C was 1.96% (±1.5) (median 1.35%) (Fig. 2B). Among the fourteen subjects, ten were treated with basal-bolus insulin therapy prior the study (three subjects with Type-1 diabetes and seven with Type-2). In this subset, mean A1C was 10.2% (±2.2%) at the beginning of the study and 8.0% (±1.6%) by the end of the study, similar to the entire study population ($p = 0.7$ and $p = 0.9$, respectively).

Eleven of the fourteen subjects experienced at least one episode of minor hypoglycemia (glucose ≤65 mg/dl) during the study (14 subjects with readings <70 mg/dl). No episodes of severe hypoglycemia were documented. Fifty-six readings of glucose ≤65 mg/dl (22.7 events per patient-year) were recorded in the eleven subjects with Type-2 diabetes (31 readings of glucose ≤60 mg/dl corresponding to 12.6 events per patient year; 83 readings of glucose <70 mg/dl corresponding to 33.7 events per patient year). Twenty-three readings of glucose ≤65 mg/dl (42.7 events per patient-year) were recorded in the three subjects with Type-1 diabetes (13 readings of glucose ≤60 mg/dl corresponding to 24.1 events per patient-year; 32 readings of glucose <70 mg/dl corresponding to 59.4 events per patient-year). As depicted in Fig. 2A, the frequency of glucose readings ≤65 mg/dl remained stable and low between 0.14 and 0.9 events per subject per week (0.07–0.46 for glucose readings ≤60 mg/dl; 0.21–1.23 for glucose readings <70 mg/dl) throughout the duration of the study, unrelated to the average glucose which improved significantly.

4. Discussion

This pilot study aims at reconciling the highly controversial topic—are glucose readings alone sufficient to provide effective and safe weekly insulin dosage adjustments? The answer to this question is immeasurably imperative for immerging technology that strives to advance the success rate of insulin therapy. Insulin dosage modifications, made by the study Endocrinologist were effective and safe despite the lack of direct personal interaction, as evidenced by the improvement in weekly mean glucose and A1C while maintaining low frequency of minor hypoglycemia. To explore the minimal clinical data required to make these safe and effective adjustments, we compared the recommendations made by the study Endocrinologist to the ones made by dedicated software. This software was generated before the study and designed to use only glucose readings to deliver recommendations for dosage adjustments; thus, it could not have been biased by confounding variables. In more than 99% of the cases the software made similar adjustments to the study Endocrinologist and no hazardous disagreements were found. Since the software was not exposed to any additional parameters like patients' comments on log sheets, the correlation between its recommendations and the ones made by the Endocrinologist corroborates that only glucose readings were necessary to improve glycemia.

The mean weekly glucose formed almost a linear trajectory from week one to week nine (Fig. 2A), until it balanced around the goal. This phenomenon supports the assertion that habitual insulin

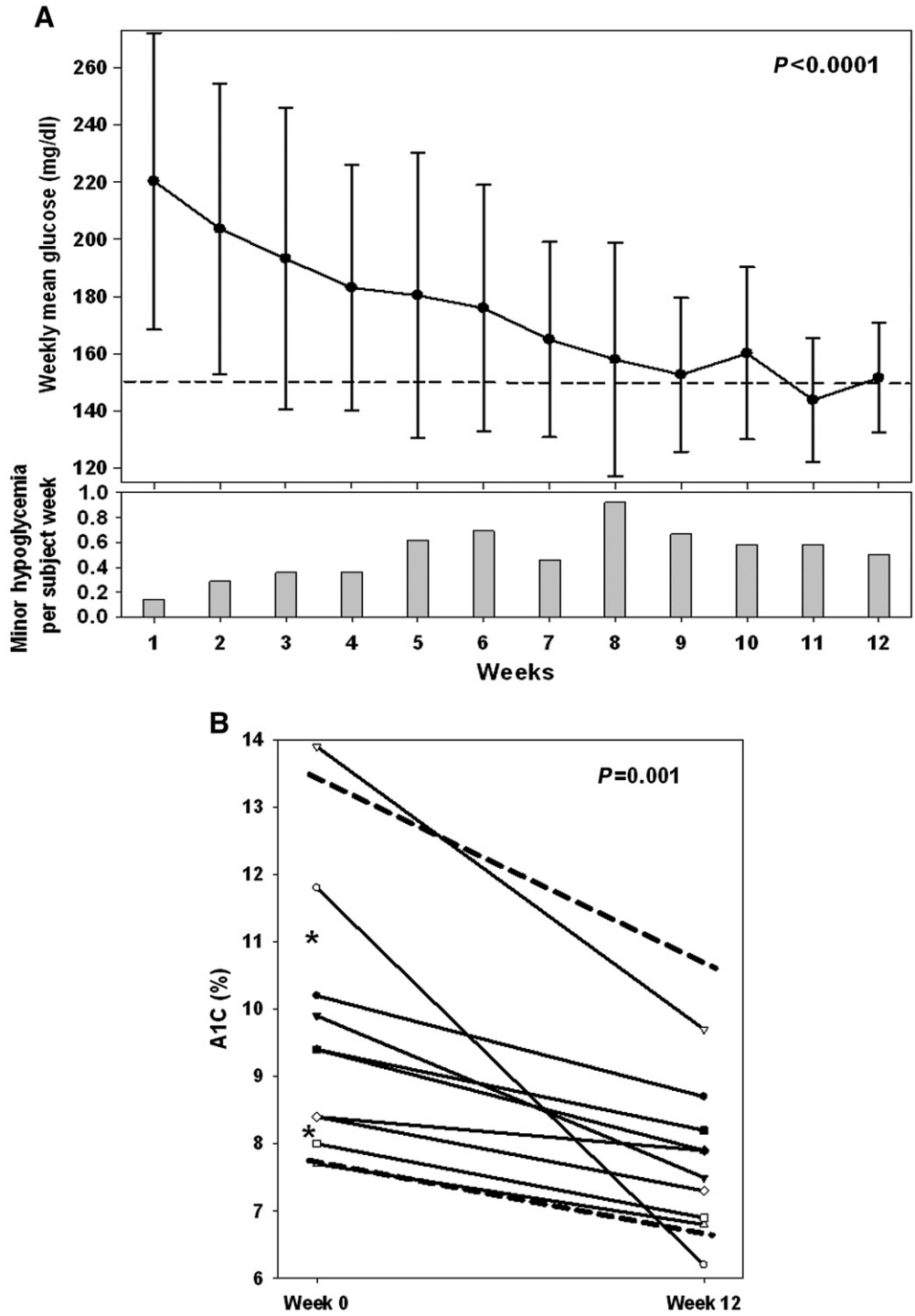

Fig. 2. A1C, mean weekly glucose, and frequency of hypoglycemia during the study period. A) Weekly mean glucose levels during the study (upper graph) and frequency of minor hypoglycemia, expressed in events per patient per week (lower graph). B) A1C changes for each subject between week one and week twelve. Solid lines depict subjects with Type-2 diabetes, dashed lines depict subjects with Type-1, and asterisks depict initial A1C of the two withdrawn subjects. Weekly insulin dosage adjustments for twelve weeks resulted in an improvement of mean glucose and A1C. Despite a superior glycemic control, the frequency of hypoglycemia remained low during the study.

titrations and not initial dosage provided in week one, were the cause for improved glycemia. Due to the gradual improvement in weekly mean glucose and the relatively short duration of the study, the final A1C likely misrepresented the improved average glucose achieved by the end of the study (Nathan et al., 2008). It would have been expected that additional 4–8 weeks of follow-up would have resulted in much lower A1C levels, provided that average glucose levels were kept similar to the ones during the last 4 weeks of the study (around 150 mg/dl).

Of the fourteen participants, ten were treated with basal-bolus therapy prior to their enrollment. This subset of patients had similar improvement in A1C compared to the entire study population, indicating that insulin titration and not insulin Types, was the reason for metabolic improvement. Only minor hypoglycemic events were recorded during the study and their frequency was low. Similar frequencies have been routinely demonstrated in clinical studies incorporating frequent insulin dosage adjustments (Davidson and Lewis, 2000; DeVries et al., 2002; Doyle et al., 2004; Holman et al.,

2008; Tsui et al., 2001, 2002). In reality, insulin titrations are done every three to six months, predominantly during outpatient clinic appointments. Consequently, hypoglycemic events are reviewed in a retrospective manner. As the main risk factor for hypoglycemia is prior hypoglycemic events, it is not surprising that outside the realm of clinical trials the frequency of hypoglycemia is in fact higher (Donnelly et al., 2005).

The main weakness of this pilot study was its relatively small subject number ($n = 14$) and short follow-up (3.25 patient year). Yet, since the investigated parameter was the process of insulin dosage adjustments the actual "N" value was considerable ($N = 568$).

Although we fully acknowledge the impact of diet and exercise on diabetes management, the data presented suggest that glucose readings alone are sufficient to enable effective and safe insulin dosage optimizations, provided that dosage adjustments are made on a weekly basis. In today's reality with the overwhelming workload in clinics, lack of care providers trained in insulin titration, and inadequate reimbursement, make frequent insulin dosage adjustments in a clinical setting unrealistic. Consequently, only 35% of insulin-treated patients achieve A1C<7% (Hoerger et al., 2008; Koro et al., 2004). Pending a planned larger study, we postulate that such software has the capacity to enable patients to safely adjust their insulin dosage between clinic appointments, realizing the full benefit of their insulin regimens for optimal glycemic control (Diabetes_prevention_trial-type_1_diabetes_study-group, 2002, The_writing_team_of_the_DCCT, 2002).

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