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ORIGINAL ARTICLE

Development and Validation of a Computer Application to Aid the Physician's Decision-Making Process at the Start of and during Treatment with Insulin in Type 2 Diabetes: A Randomized and Controlled Trial

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Abstract

Background:

Achieving optimum blood glucose control in patients with type 2 diabetes mellitus (T2DM) is difficult. Some primary care physicians (PCPs) delay the start of insulin use because of the uncertainty in intensifying insulin therapy. The objective was to develop and validate a computer application (CA) that helps PCPs to make decisions about insulin therapy in order to achieve a significant improvement in glycated hemoglobin (HbA1c).

Methods:

This was a cluster-randomized clinical trial. Fourteen primary care centers (PCCs) in Madrid with 66 PCPs and 697 T2DM patients on insulin therapy were randomly divided into two groups of seven PCCs each. In the intervention group, seven PCCs included 39 PCPs and 365 T2DM patients on insulin therapy. These PCPs were free to use the CA. A further seven PCCs were assigned to the control group with 27 PCPs and 332 T2DM patients on insulin therapy. The control group did not use the CA. The duration of the trial was 18 months to validate the CA. The outcome was a change in HbA1c from baseline.

Results:

In the intervention group, the final HbA1c was 7.19% (standard deviation [SD] ± 0.93), with a difference from the start of -0.69% (p = .001). In the control group, it was 7.71% (SD ± 1.37), with a difference from the start of -0.09% (p not significant).

Conclusions:

This CA helps to improve HbA1c figures of T2DM patients with insulin when it is used by PCPs to make decisions when starting, continuing, or changing insulin and its dosage.

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Abbreviations: (ADA) American Diabetes Association, (CA) computer application, (HbA1c) glycated hemoglobin, (IDF) International Diabetes Federation, (PCC) primary care center, (PCP) primary care physician, (SD) standard deviation, (T2DM) type 2 diabetes mellitus

Keywords: automated treatment, clinical trial, computer application, decision making, dynamic dosage, medical software, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a disease that causes hyperglycemia and vascular complications.[1] The American Diabetes Association (ADA) defines glycated hemoglobin (HbA1c) <7% and a level of preprandial glycemia <130 mg/dl and postprandial <180 mg/dl as a good level of control.[2,3]

However, surveys in the United States, United Kingdom, Sweden, and Holland show that, in more than 50% of patients, glycemic control is not achieved.[4,5] Primary care physicians (PCPs) have little time to make decisions about whether to start, continue, or change the insulin doses when they treat a large number of patients.[6] Furthermore, patients are concerned about the side effects of insulin, which include hypoglycemia and weight gain.[7,8]

There is also a certain clinical inertia that makes physicians and patients with moderate control (close to but not <7%) delay the start of insulin therapy for as long as possible.[9,10] Some physicians recognized the indecision in choosing the right insulin course for each patient and the difficulty in dosing the insulin.[11,12] Nowadays, physicians have a much wider range of insulin on offer but also greater difficulties in deciding which one best adapts to a particular patient.[13]

The objective of this trial was to design and scientifically validate a computer application (CA) to help PCPs make decisions about the insulin handling of T2DM patients in an outpatient environment. This support includes the start, continuation, and adjustment of up to five daily insulin injections and each of their doses. The validation is obtained through achieving better metabolic control of these patients (measured as a reduction of HbA1c of at least 0.6%).

Methods

A computer company developed the CA on a Microsoft.NET platform that manages a Microsoft Access database on the physician's computer. It contains (1) the patient's demographic data, (2) glycemia profiles, and (3) recommendations to the physician. In order to make decisions to change the insulin standard and the dosage for a specific patient, the PCP has the freedom to choose between their own professional criteria or accept the automated recommendations offered by the CA.

The design was a controlled, random trial. The trial was carried out by PCPs who work in the primary care center (PCC). The physicians work in the National Health Service, Madrid, Spain. Fourteen PCCs were selected from an urban area wherein every PCP has a quota of 1800 patients, of which, approximately 100 are patients with T2DM. The randomization unit was the PCC. They were randomly divided into blocks of seven. Seven PCCs were assigned to the intervention group and seven to the control group. The process was supervised by the Epidemiology Service and the Ethics Committee of the "Puerta de Hierro" University Hospital, Majadahonda, Madrid, Spain. All research activities were performed in accordance with the World Medical Association's Declaration of Helsinki. Informed consent was obtained from all participants.

The algorithms interactively included the following matters: (1) profiles of seven points of glycemia introduction obtained by self-monitoring, (2) seven guidelines of insulin therapy, and (3) up to three final insulin therapy recommendations for each initial insulin therapy regimen applied to each glycemia profile (see **Table 1**).

1. The profile for seven glycemia points included glycemia before breakfast, lunch, and dinner and 2 h after breakfast, lunch, and dinner. It also included early morning glycemia, when it was checked. For each glycemia point, four ranges of control were defined: bad (B), regular (R), good (G), and hypoglycemia (H). The figures of the preprandial ranges (in mg/dl) were bad >180, regular 131–180, good 80–130, and hypoglycemia <80. Two hours after ingestion, the ranges were bad >230, regular 181–230, good 100–180, and hypoglycemia <100. Early morning glycemia figures >100 were considered good, and those below this were considered to be suspected hypoglycemia (see **Table 2**). These ranges of mg/dl have been based on the work of Rohlfing and colleagues[3] and have been adapted to this clinical trial. A total of 4096 different profiles were developed, starting in B, B, B, B, B, B, B (all data in the seven-point profile show bad glycemic control) up to H, H, H, H, H, H, H (all data show hypoglycemia).

2. The algorithms were built to reflect the following seven general guidelines of insulin therapy: 2.1, starting insulin; 2.2, intermediate or basal insulin once or twice a day; 2.3, basal insulin and mixed

insulin on the same day; 2.4, mixed insulin twice a day; 2.5, mixed insulin twice a day plus a dose of rapid-acting insulin before lunch; 2.6, mixed insulin three times a day; and 2.7, basal-bolus guideline (includes guidelines with intermediate or basal insulin once or twice a day, plus one, two, or three doses of rapid-acting insulin). The CA includes a table with the combinations of rapid-acting, basal, and mixed insulin with 25%, 30%, 50%, and 70% of rapid-acting insulin, up to a maximum of five daily injections (a maximum of two different insulin injections at breakfast, one at lunch, and a maximum of two different insulin injections at dinner or at bedtime).

Table 1.
Algorithm Examples[a]

Current insulin		Glycemia control						Insulin treatment proposal
		Before breakfast	2 h later	Before lunch	2 h later	Before dinner	2 h later	Choose one of the following options:
Example 1:		R	B	R	R	G	B	Option 1: Breakfast: rapid 4ui Dinner or BT: basal 22 U Option 2: Breakfast: mix 70/30 13 U Dinner: mix 70/30 11 U
Breakfast:	-							
Breakfast:	-							
Lunch:	-							
Dinner:	-							
Dinner/BT:	Basal 20 U							
Example 2:		R	B	R	R	G	B	Option 1: Breakfast: mix 70/30 23 U Dinner: mix 70/30 11 U Option 2: Breakfast: mix 70/30 22 U Lunch: rapid 3 U Dinner: mix 70/30 11 U Option 3: Breakfast: mix 70/30 14 U Lunch: mix 70/30 8 U Dinner: mix 70/30 11 U
Breakfast:	Mix 70/30 20 U							
Breakfast:	-							
Lunch:	-							
Dinner:	Mix 70/30 10U							
Dinner/BT:	-							
Example 3:		R	B	R	R	G	B	Option 1: Breakfast: basal 22 U Breakfast: rapid 7 U Lunch: rapid 3 U Dinner: rapid 9 U Option 2: Breakfast: mix 70/30 20 U Dinner: mix 70/30 15 U
Breakfast:	Basal 20 U							
Breakfast:	Rapid 6 U							
Lunch:	-							
Dinner:	Rapid 8 U							
Dinner/BT:	-							

[a] Glycemia control: B, bad; R, regular; G, good; H, hypoglycemia. Basal, basal insulin; BT, bedtime; Mix 70/30, insulin mix 70% basal/30% rapid.

Table 2.
Ranges of Glycemia Control[a]

Range	Before breakfast	2 h later	Before lunch	2 h later	Before dinner	2 h later	Early morning
Bad	>180	>230	>180	>230	>180	>230	
Regular	131–180	181–230	131–180	181–230	131–180	181–230	
Good	80–130	100–180	80–130	100–180	80–130	100–180	≥100
Risk of hypoglycemia	<80	<100	<80	<100	<80	<100	<100

[a] All numbers in mg/dl.

3. The design of the algorithms included the recommendation to change the dose and also the insulin regimen when necessary, e.g., from mixed insulin twice a day to another more appropriate standard for a specific patient, such as the basal-bolus guideline, or *vice versa*.

The algorithms were based on the clinical practice guides of the ADA,[2] the International Diabetes Federation (IDF),[14] and the American Association of Clinical Endocrinologists.[15] However, when these algorithms did not offer solutions to each insulin regimen, that part of the algorithm was designed by the authors specifically for this CA and were based on clinical experience of the consultant endocrinologist. In general, the dose was increased by 15% when the average glycemia in the ranges was bad, 10% if it was regular, and it was kept the same if it was good. If hypoglycemia was present, the dose was reduced by 15%. At this point—and based on the mentioned percentages—a mathematical algorithm was created to provide each recommendation with its corresponding dose. Finally, to cover all possible insulinization regimens with which a patient could come to the physician's clinic, applied to the 4096 possible glycemia profiles, it was necessary to develop 75,000 recommendations to include every particular case of insulin therapy.

Both groups of physicians (intervention and control) were given a short course on diabetes and insulinization.

Outcome

The main result was the change in the HbA1c figure from baseline to the end of the trial. The HbA1c was recorded every 3–6 months. If the patient did not complete the study and had two determinations of HbA1c, the last one was taken as the final HbA1c.

Calculating the Sample Size

With the supposition that the intra-aggregate correlation did not exceed 0.10 for aggregates with an average size of 30 patients with insulin per physician, the sample size to detect a difference in HbA1c between the two groups at the end of the monitoring period of 0.60%, for an expected standard deviation (SD) of 2.1%, an alpha value of 0.05, a statistical power of 80%, and losses in the monitoring of no more than 18%, there are 590 patients, which implies the random division of at least 20 physicians per group.[16]

Statistical Analysis

The comparisons are based on the Student's *t*-test. The similitude was studied between groups in basal. To evaluate the results, the change in HbA1c was used.

All the analyses were carried out by principle of treatment assigned. The level of statistical significance was 0.05, in bilateral contrast. In all cases, the SD was described as a measure of dispersion.

Before the trial, an endocrinologist and a PCP used and corrected the program to unify criteria considering a good level of agreement when the Kappa index was >0.8 (substantial agreement).[17]

External Validation Process

For 18 months, all the PCPs used as usual their best clinical abilities in making decisions in insulin therapy, but only the PCP in the intervention group had access to the CA.

Results

Fourteen PCCs took part, with 66 PCPs and 697 T2DM patients on insulin therapy. Of these, seven PCCs, with 39 PCPs and 365 T2DM patients, were assigned to the intervention group. Seven PCCs, with 27 PCPs and 332 T2DM patients on insulin therapy, were assigned to the control group (see **Table 3**).

Table 3.
Baseline Clinical Characteristics of Patients on Insulin Therapy[a]

	Intervention group *n* = 365	Control group *n* = 332
Age	68.5 ± 7.3	68.3 ± 8.8
Female (%)	157 (42.9)	145 (43.8)
Male (%)	208 (57.1)	187 (56.2)
HbA1c (SD)	7.88 (1.38)	7.80 (1.52)
BMI (kg/m^2)	29.2 ± 4.1	29.8 ± 4.5
Daily dose of insulin U (SD)	13.63 (4.43)	13.53 (4.39)
Only insulin therapy (%)	225 (61.6)	209 (62.9)
Insulin plus oral antidiabetics (%)	140 (38.3)	123 (37)
Oral antidiabetics (%): Metformin Sulfonylureas Glitazones DPP-4 inhibitors	 130 (35.5) 13 (3.5) 0 (0) 8 (2.1)	 116 (34.8) 10 (2.9) 0 (0) 5 (1.4)
Two oral antidiabetics (%)	11 (2.8)	8 (2.2)

[a] No statistical differences between groups for any item. BMI, body mass index; DPP-4, dipeptidyl peptidase-4.

Both groups were comparable in demographics and clinical characteristics. They were also comparable in insulin monotherapy, units of insulin, and concomitant use of oral antidiabetics. There were no statistical differences between both groups (see **Table 3**).

Glycated Hemoglobin in Diabetes Patients with Insulin Therapy, Intragroup Comparison

In the intervention group, the HbA1c inpatients with insulin was 7.88 (SD ± 1.38) at baseline and 7.19 (SD ± 0.93) at the end of the trial, with a difference of -0.69 (p = .001). In the control group, they were 7.80 (SD ± 1.52) at baseline and 7.71 (SD ± 1.37) at the end of the trial, with a difference of -0.09 (p not significant; see **Table 4**).

Glycated Hemoglobin in Diabetes Patients with Insulin, Comparison between Groups

The difference at the end of the trial in HbA1c between the intervention and control groups was -0.52 (p = .01), whereby the best result was achieved in the intervention group (see **Table 4**).

Daily Doses of Insulin

At the start, the average units of insulin received by the patients were similar in both groups, 13.63 U (SD ± 4.43) in the intervention group and 13.53 U (SD ± 4.39) in the control group (p not significant). At the end of the trial, both groups increased their doses of insulin to 22.62 U (SD ± 7.20) and 14.72 U (SD ± 5.83), respectively. The increase in the intervention group of +8.99 U was significant. The difference between the groups was 7.9 U of insulin more in the intervention group than in the control groups (p < .01; see **Table 5**).

Table 4.
Differences in Glycated Hemoglobin in Diabetes Patients with Insulin

	Baseline HbA1c % (SD)	End of the trial HbA1c % (SD)	Difference intragroup
Intervention	7.88 (1.38)	7.19 (0.93)	-0.69, p = .001
Control	7.80 (1.52)	7.71 (1.37)	-0.09, p not significant[a]
Difference between groups	-0.08, p not significant[b]	-0.52, p = .01	

[a] Not significant, intragroup comparison
[b] Not significant, comparison between groups.

Table 5.
Daily Dose of Insulin in Units

	Baseline average (SD)	End of the trial average (SD)	Difference intragroup
Intervention	13.63 (4.43)	22.62 (7.20)	8.99, p = .001
Control	13.53 (4.39)	14.72 (5.83)	1.19, p not significant[a]
Total	p not significant[b]	-7.9, p < .01	

[a] Not significant, intra-group comparison
[b] Not significant, comparison between groups.

Discussion

We have developed a CA (InsulinSmart) for insulin treatment in T2DM patients. This application has been designed as a tool to help PCPs. The patients of the physicians who used the CA in the insulin treatment of their patients obtained a reduction (-0.69%) in their HbA1c compared with the patients of the physicians who did not have access to the CA. The benefit obtained was statistically significant but clinically moderate, as the patients reduced their HbA1c but did not go below the desired 7%.

The CA has been designed to be very simple and quick to use in daily practice; however, its development was more complex. By establishing four ranges of control of the glycemia (hypoglycemia, good, regular, and bad), it was necessary to develop 4096 different glycemia profiles. Given that there are multiple insulin regimes that a patient can use—41 different insulin therapy regimes were identified—it was necessary to develop 75,000 treatment recommendations.

In the case of some insulin combinations, such as the basal-bolus strategy, the glycemia profile used only included four glycemia determinations (before breakfast and 2 h after breakfast, lunch, and dinner). It was decided to use this summarized type of glycemic profile based on the stepwise strategy and the basal plus strategy.[18,19]

In some cases, with important hyperglycemia after breakfast, lunch, or dinner, it was decided to create up to three possible treatment options for the same glycemia profile. In general, these three options offer the physician a recommendation with a basal-bolus standard (with rapid-acting insulin one, two, or three times a day, as appropriate), a recommendation with mixed-rapid-mixed insulin, and, finally, a recommendation with mixed-mixed-mixed insulin.

As the physicians had three different options available, they had more choice, and they may feel more encouraged to use the program again with the next patient. Furthermore, the PCP can learn more or strengthen insulinization guidelines that may have previously involved certain doubt.

For instance, a widely used guideline is the addition of basal insulin to the prior treatment with oral agents. This strategy is based on the optimum control of basal glycemia. However, a significant proportion of patients do not manage to reach the objective of HbA1c < 7% due to postprandial hyperglycemias. For that reason, the next step in the intensification of treatment can be the addition of a dose of rapid-acting insulin before the main meal, or meal that generates the greatest hyperglycemia (basal plus and stepwise strategies), maintaining the prior treatment with basal insulin and oral agents. If it is necessary, additional injections of rapid-acting insulin can be progressively introduced later on.

An added problem is that, besides offering changes in the types of insulin and number of insulin injections every day, the doses needed to be adapted to the needs of the glycemia profiles. This was carried out by building a dynamic dosage algorithm that combined the previous doses, the previous types of insulin, the final types of insulin, and the need to increase or reduce the dose depending on the glycemia profile on which the treatment option is applied.

The authors recognized some limitations in the study. First is the discussion of algorithms available in the literature. In this sense, it must be said that it is not an objective of this publication to systematically review the literature, and therefore, the authors will not go beyond referring to the publication of algorithms by the ADA, the European Association for the Study of Diabetes, the IDF, the American Association of Clinical Endocrinologists, and other more local initiatives.

However, the authors believe that these algorithms mentioned earlier are too general and do not really help the PCP without the help of a close colleague—as often happens in primary care—when faced with an insulin regime with which he is not familiar. In fact, in this study, and to cover much of the reality of the prescription of insulin, the authors have had to include 75,000 different recommendations.

Second, some of the patients were included after the trial started. In the setting in which we have developed this trial, doctors took care of all diabetes patients in their clinic, including those included in the trial. From the pool of all diabetes patients, those who initiated insulin after starting the trial were also included in the trial. We thought that the increase in the number of patients treated with insulin could be an outcome that reinforces the value of the CA.

However, there were no final differences between the two groups regarding the number of patients who were treated with insulin. It appears that the CA did not significantly encourage the doctors to include a larger number of diabetes patients with insulin to be treated. Notwithstanding, the CA could be positively responsible for the increasing insulin dose seen in the patients of the intervention group. The improvement of HbA1c in this last group is perhaps due to the fact that the physicians felt more secure in their decisions with the backing from the CA and hesitated less in increasing the dose when necessary.

Third, physicians were trained to register data of hypoglycemia, severe or not, although, by the end of the trial, no cases were registered. It was not statistically affordable for us to work with data of hypoglycemia when doctors seem to have been reluctant to suspect, confirm, and register hypoglycemia episodes. It is possible that they did not give importance to signs or symptoms of mild hypoglycemia. In the end, we did not include this data, though no serious cases were reported.

Other limitations are that it depends on the physician's desire to use the CA or not, and in an environment of an excessive workload and lack of time, the physician may opt not to consult the software. In patients who used insulin, we know how many patients there were before and at the end, but unfortunately, we have no information on the patients who suspended or abandoned the treatment with insulin, nor do we have information on the changes made in the types of insulin.

It is surprising the thousands of possibilities that a physician who makes decisions on insulin therapy must contemplate, besides being familiarized with the possible insulin combinations with which the patient arrives at and with which the patient can leave the clinic. In addition, the physician must calculate the leaving dose, which will be based on the arrival dose.

Therefore, it is not surprising that PCPs have doubts or even fears regarding starting or intensifying insulin therapy. However, they must be willing to do so because there are not enough endocrinologists in the health care

environment to tackle the number of visits needed by patients with T2DM who require insulin. This CA will be able to help them.

The contribution of new technologies to help in the medical decision-making process is a milestone in promoting the use of scientific evidence in clinical practice. We have demonstrated that linking technology and computing in clinical decisions can be useful. Matching technology with treatment decisions can help physicians to resolve clinical problems and, above all, to optimize the patients' health results.

This CA has demonstrated its external validity. This means that a new technology (impact of technological development associated with a group of medicines) will help to optimize the start and the continuation of insulinization (impact of the health care) and the fulfillment of objectives of good glycemic control (clinical impact).

The acceptance of the CA among physicians has been good, and in the light of their request to use the CA after the clinical trial was complete, a more simple application has been commercialized that can be downloaded to smart phones.

Conclusion

The CA has been validated. It is a useful CA as an aid for physicians when starting, continuing, and changing the type of insulin and its dose and in reducing HbA1c.

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