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RESEARCH ARTICLE

Effect of Incorporating Computerized Insulin Dose Adjustment Algorithms into a Remote Patient Monitoring Program on HbA1c Levels in Patients with Type 2 Diabetes

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ABSTRACT

Aims: To evaluate the effect of Federal Drug Administration-cleared computerized insulin dose adjustment algorithms (CIDAAs) incorporated into a Remote Patient Monitoring (RPM) program on HbA1c levels.

Material & Methods: Type 2 patients receiving insulin for >6 months with HbA1c levels ≥8.0% enrolled in a Medicare Advantage plan were recruited into 3 arms; Group A (RPM plus CIDAAs, N=40), Group B (RPM but no CIDAAs, N=42), and Group C (usual care with no RPM or CIDAAs, N=33). In Groups A and B, glucose readings of >200 mg/dL and <70 mg/dL triggered alerts and health educators contacted patients for counseling to avoid future episodes.

Results: Baseline HbA1c levels (% ± SD) were not statistically different among Groups A (9.5 ± 1.5), B (9.2 ± 1.1) and C (9.0 ± 0.9). At 6 months, HbA1c levels fell twice as much in Group A (-1.5 ± 1.0) as in Groups B (-0.7 ±1.5) and C (-0.7 ± 1.2) (P <0.001). Alerts >200 mg/dl were significantly less in Group A (N=942) than in B (N=1111) (P = 0.002) but alerts <70 mg/dL were not significantly different (235 vs 209). In Group A, baseline per patient daily insulin doses of 78 units rose 40% to 109 units. Six patients in Group C had emergency room visits for hypoglycemia but none in Groups A and B.

Conclusions: The RPM program lessened clinical hypoglycemic risk but required CIDAAs to markedly increase insulin doses effectively and safely to significantly lower HbA1c levels twice as much as either RPM alone or usual care.

Keywords Computerized Insulin Dose Adjustment Algorithms; Remote Patient Monitoring; Remote Glucose Monitoring; Insulin Therapy

INTRODUCTION

Diabetes is a serious disease affecting 11.3% of the United States population[1] with devastating micro-vascular complications. Diabetic retinopathy is the leading cause of blindness in the working age population.[2] Diabetes is the leading cause of end stage renal disease in the United States[3] with over one-half of the patients receiving dialysis because of diabetic nephropathy. Lower extremity amputations, due mostly to foot ulcers secondary to diabetic peripheral neuropathy, are 8-fold higher in people with diabetes. Tragically, these complications do not have to occur. Five studies in people with both type 1[4-6] and type 2[7,8] diabetes have demonstrated that if HbA1c levels can be lowered to <7% early in the course of the disease and maintained, development or progression of these diabetic complications do not have to happen. Unfortunately, over half of people with diabetes have HbA1c levels >7.0%.[9]

Patients with type 1 diabetes, affecting approximately 5% of people with diabetes, require insulin. Patients with type 2 diabetes, affecting approximately 90% of people with diabetes, rarely do initially. They can be controlled, usually for a number of years, with non-insulin drugs. However, endogenous insulin secretion progressively decreases in these individuals until many of them are unable to be controlled on non-insulin drugs alone and require insulin.

Primary care clinicians (PCCs), i.e., those making independent clinical decisions because of their licensure or following approved protocols, are responsible for diabetes care in 90% of people with diabetes.[10] The most recent data from the Centers for Disease Control and Prevention[1] are that there are 37.3 million people in the United States who have diabetes. Of these, 28.7 million are diagnosed, which means that PCCs provide diabetes care to 25.8 million. Thirty percent of people with diabetes take insulin[11] which yields 7.7 million receiving insulin, the vast majority of whom are managed by PCCs.

PCCs are challenged using insulin. It took 3 to 7 years to start insulin once people with type 2 diabetes had failed maximal doses of 2 or 3 non-insulin, anti-diabetes drugs with HbA1c levels of >8.0%.[12,13] When insulin was started, the range of HbA1c levels was 8.9% to 9.8% with a mean of 9.3%.[12-16] The mean HbA1c level was 9.7% when insulin was intensified in patients failing basal insulin alone.[13,16] Insulin intensification occurred in only 25-30% of patients and insulin was discontinued in a similar number.[16-24] The average range of HbA1c levels was 7.9% to 9.3% with a mean of 8.5% in patients receiving insulin in the United States.[14,24,25]

Mellitus Health has developed computerized insulin dose adjustment algorithms (CIDAAs) to help PCCs adjust insulin doses. In a pre– post study[26], a nurse practitioner utilizing these algorithms lowered HbA1c levels from 10.0% to 7.6% in 6 months in poorly controlled, minority patients who measured their glucose levels remotely. In another pre- post study,[27] a clinical pharmacist utilizing these algorithms lowered HbA1c levels from 11.5% to 8.3% and increased time in range from 29% to 51% after a mean of 3 months in a similar population who used continuous glucose monitoring. The current study is a randomized clinical trial comparing these algorithms used in patients who were enrolled in a Remote Patient Monitoring (RPM) program with 2 control groups, one also enrolled in the RPM program but whose PCCs did not have access to the algorithms and the other not enrolled in the RPM program (Usual Care).

METHODS

This study took place in a Health Maintenance Organization, Intermountain Healthcare Nevada, which is a multi-specialty physician group. The population studied was enrolled in a Medicare Advantage plan. Some insurance plans automatically enrolled patients in an RPM program (Harmonize Health) while other insurance plans did not cover an RPM program. In the RPM program, glucose levels were measured remotely and sent to a Health Insurance Portability and Accountability Act (HIPAA)-approved portal. PCCs did not routinely receive these glucose readings but when a value was <70 mg/dL or >200 mg/dL, health educators were alerted and contacted patients to counsel them on how to avoid subsequent episodes. Health educators also sent these alert values to the patient's PCC who could access more glucose readings if they wished.

Patients with type 2 diabetes eligible for this study had to be receiving insulin for at least 6 months and have an HbA1c level ≥8.0%. Those identified as being eligible were asked whether they would be interested in participating in a research study. Patients who agreed and were enrolled in the RPM program were randomized by having every other one assigned to either Group A in which the CIDAAs (Insulin Insights™) were available to PCCs or Group B in which Insulin Insights™ was not. Patients who agreed but were not covered to be in the RPM were assigned to Group C which was designated as Usual Care. Patients in Group A and Group B had to sign informed consents but the Institutional Review

Board (Advarra IRB) agreed that those receiving usual care did not. Patients in Group A and Group B utilized a Bionime™ Bluetooth glucose meter whose blood glucose readings were sent to the RPM program at Harmonize Health. All blood glucose readings from Group A patients were also analyzed by Insulin Insights™. Patients in Group C continued to use their own off-study glucometers (not Bionime™). Patients in Group A and Group B were not supposed to receive additional non-insulin, anti-diabetes drugs throughout the study whereas there were no such restrictions on their introduction in patients in Group C. However, some patients in Groups A and B did have non-insulin, anti-diabetes drugs added or discontinued by PCCs not involved in adjusting insulin doses (see below).

Insulin Insights™ is FDA cleared (and CE mark registered). The initial registration of a patient requires on a one-time basis only the following information; year of birth, height, weight, sex, insulin regimen (types of insulin, when given and doses), approximate time range for each meal and bedtime and pre- and postprandial targets set by the PCC. However, for this study, preprandial and postprandial target ranges were set at 70-130 mg/dL and 120-180 mg/dL, respectively. Reports generated by Insulin Insights™ were not sent to patients but to 3 PCCs (2 physicians and a physician assistant). The reports contained a scatterplot of all the glucose readings related to time in the 24-hour cycle, the organization of the glucose readings into before and after each meal and before bedtime values, an analysis of the readings during each period of the 24-hour cycle (overnight, morning, afternoon and evening) and recommendations for adjustment of insulin doses (if necessary) that the PCCs could accept or modify. Once the PCC decided on the new doses (or continued the previous doses because the recommendations made no suggestions for change), these doses served as the basis for the next report. Reports in Group A patients were generated every 2 to 3 weeks. If glucose values by the end of 2 weeks indicated that at least one insulin dose adjustment was necessary, a report was sent at that time. If there were no indications of a need for a dose adjustment at 2 weeks, a report was sent between 2 and 3 weeks as soon as a dose adjustment was indicated or at 3 weeks if none were.

The primary outcome was the change in HbA1c levels from baseline to 6 months. A secondary outcome in Groups A and B was the number of high (>200 mg/dL) and low (<70 mg/dL) alert values during the study. Another secondary outcome was the number of severe hypoglycemic events requiring an emergency room (ER) visit. The 3 PCCs who adjusted the insulin doses in Group A patients were surveyed at the end of the study regarding the time spent in deciding on dose changes in their own patients before the study began and in arriving at dose change decisions using the reports from Insulin Insights™.

Baseline HbA1c levels were analyzed by a non-parametric one-way ANOVA. Changes in HbA1c levels were analyzed by Dunn's test for multiple differences. The number of patients receiving a new non-insulin, anti-diabetes drug was analyzed by Chi square tests. Alert values were analyzed by an asymptomatic test of homogeneity for the Poisson rates from 2 groups. Significance was accepted at $P < 0.05$ (2-tailed).

RESULTS

The demographic characteristics of the patients are shown in the top of Table 1 and their clinical outcomes at the bottom of Table 1 and the Figure. Because changes in insulin doses were given to the patients in Group A virtually, most of them were not seen in person at the end of the study and changes in weight could not be documented. There were no significant differences among the baseline HbA1c levels of the 3 groups. HbA1c levels fell more than twice as much in Group A (-1.5%) compared to Group B (-0.7%) and Group C (-7.0%) in which the decreases were the same. There were no visits to the ER for hypoglycemic episodes in Group A and Group B while 6 patients in Group C did make such a visit. The number of alert values >200 mg/dL were significantly less in Group A vs Group B during the study while the number of values <70 mg/dL were not significantly different.

Table 1 – Demographics and Clinical Outcomes

	Group A (N = 40)	Group B (N = 42)	Group C (N = 33)
Age (Years ± SD)	69.1 ± 8.1	67.1 ± 6.9	69.3 ± 9.7
Sex (females/males)	19/21	21/20	18/14
BMI (kg/m² ± SD)	35.4 ± 6.9	34.9 ± 7.2	36.4 ± 9.2
Baseline HbA1c (% ± SD)*	9.5 ± 1.3	9.2 ±1.1	9.0 ± 0.9
Six Month HbA1c (% ± SD)	8.0 ± 1.0	8.5 ± 1.6	8.3 ± 0.9
HbA1c Change (% ± SD)†	-1.5 ± 1.0	-0.7 ± 1.5	-0.7 ± 1.2
All alerts (N)‡	1177	1320	-
Alerts >200 mg/dl (N)§	942	1111	-
Alerts <70 mg/dl (N)‖	235	209	-
ER Visits (N)	0	0	6

N - Number of patients; ER – Emergency Room; *Groups A, B and C, P = 0.20; †Group A vs B, P = 0.001, Group A vs C, P = 0.001, Group B vs C, P = 0.37; ‡Group A vs B, P = 0.02; §Group A vs B, P = 0.002; ‖Group A vs B, P = 0.14

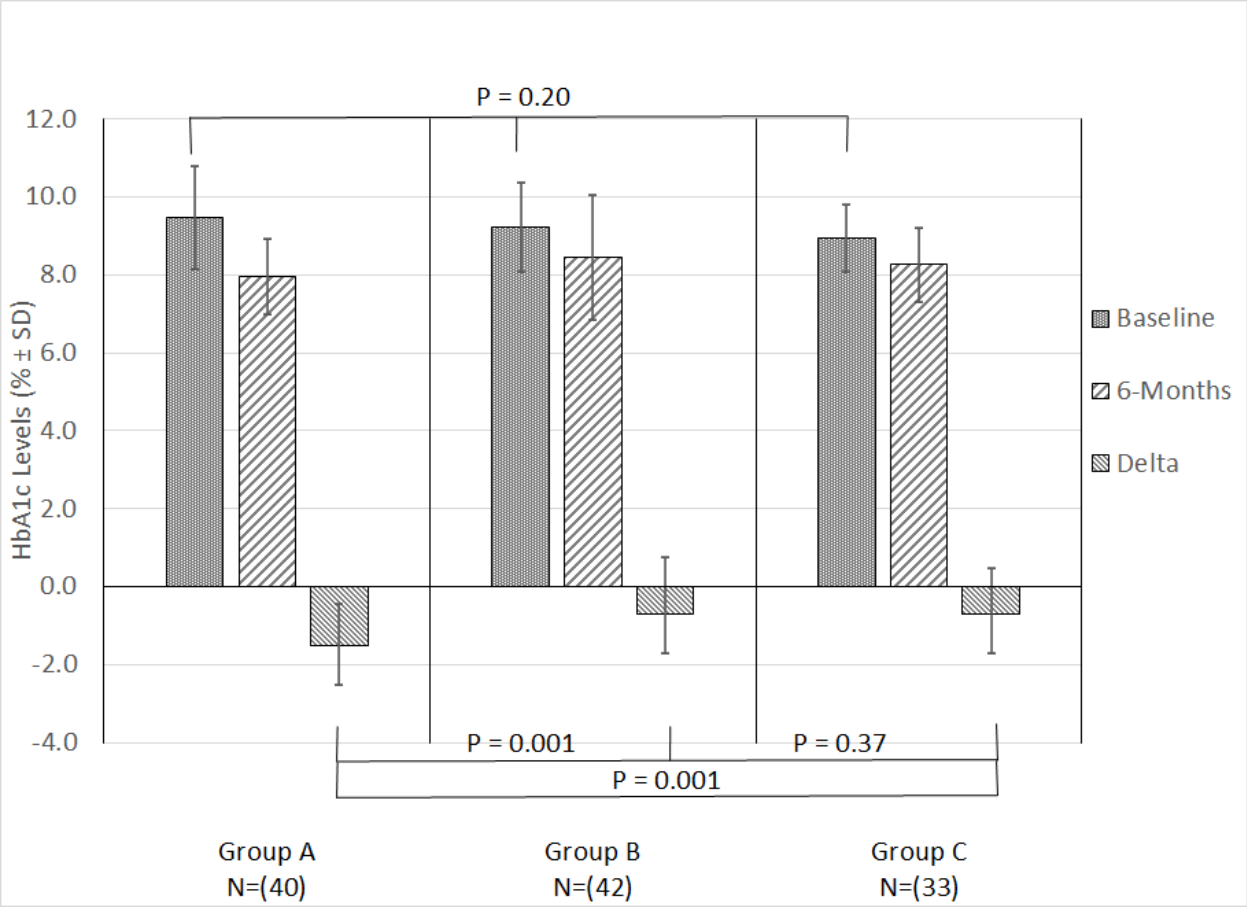

Figure: Effect of CIDAAs on HbA1c Levels Compared to RPM Alone and Usual Care.
CIDAA-Computerized Insulin Dose Adjustment Algorithms (Insulin Insights™); RPM – Remote Patient Monitoring

All Insulin Insights™ recommendations were accepted either in full or some only in part to reflect clinical judgement; no report had all of the recommendations rejected. There were 384 reports generated in the Group A patients, 256 of which contained recommendations for changes in insulin doses. The vast majority of the 128 reports in which no changes were recommended were because there were too few glucose readings to reflect the patient's usual lifestyle in any periods of the day and overnight. The PCCs accepted the recommendations in 91 reports but modified them in 165. Of the modifications, 143 were for less than the recommended total dose changes and 22

were for greater than the recommended dose changes. At the end of the study, the PCCs had increased the patients' total insulin units by only 57% of the amount recommended by Insulin Insights™. This resulted in the initial total daily amount of insulin taken per patient of 78 units rising to 109 units by the end of the study, a 40% increase. Interestingly, although 5 patients had no change and 4 patients had a reduction in their total insulin units between the initial and final reports, all of them had a decrease in their HbA1c levels ranging from -0.4% to -2.8% with a mean of -2.1%.

PCCs see their patients approximately every 3 months and continued to do so for patients in Group B and Group C during the study. However, patients in Group A were seen less frequently, every 4-6 months, during the study since their glucose readings were analyzed and recommendations made for PCCs every 2-3 weeks. Before access to Insulin Insights™, physician PCCs took 5-10 minutes to gather, organize and analyze glucose readings before deciding on insulin dose adjustments compared to 2-3 minutes during the study. For the physician assistant PCC, it was approximately 15 minutes before the study and approximately 5 minutes with access to Insulin Insights™.

The initial and final insulin regimens are shown in Table 2 and were similar among the 3 groups. However, the number of patients discontinuing non-insulin, anti-diabetes drugs and receiving new ones added to their insulin regimens was different among the 3 groups. In Group A, they were discontinued in 6 patients and added in 4, a net subtraction of -2. In Group B, they were discontinued in 4 patients and added in 10, a net addition of +6. In Group C, they were discontinued in 1 and added in 13, a net addition of +12. Compared with Group A, the number of patients receiving new non-insulin, anti-diabetes drugs in Group C was significantly increased (P = 0.003). The increase in Group B showed a trend compared with Group A (P= 0.087). The number of patients receiving new non-insulin, anti-diabetes drugs was similar between Group B and Group C (P = 0.17).

Table 2 – Anti-Hyperglycemic Medications

	Group A (N = 40)		**Group B (N = 42)**		**Group C (N = 33)**	
Insulin Regimen	Initial	Final	Initial	Final	Initial	Final
Basal alone/Bedtime NPH alone (N)	21	18	20	18	16	17
Basal/Bolus (N)	14	15	14	16	12	11
Self-Mixed Split (N)	5	6	3	3	4	4
Premixed (N)	-	-	3	3	1	1
U-500 Regular (N)	-	1	1	1	-	-
Lispro only (N)			1	1	-	-

N – number of patients

DISCUSSION

Insulin Insights™ more than doubled the improvement in HbA1c levels in patients enrolled in an RPM program compared to both those also enrolled in the RPM program but whose PCCs did not have access to the CIDAAs and those followed in Usual Care. This improvement in Group A occurred in the absence of increased hypoglycemia alert levels. There were no ER visits for severe hypoglycemic events in patients enrolled in the RPM program (Group A and Group B) whereas 6 patients in Group C required one. There was a 40% increase in insulin units in Group A by the end of the study indicating that these patients were greatly under-insulinized. The PCCs increased the patients' insulin units by only 57% of the amount recommended by Insulin Insights™, likely due to their concerns about potential hypoglycemia. However, higher adherence to the recommended insulin dose increases probably would have resulted in greater improvement. Some of the improvement in diabetes control in Groups B and C could have been due to the increased net addition of new non-insulin, anti-diabetes drugs. The same improvements in HbA1c levels in Group B and Group C suggest that simply providing lifestyle counselling around high glucose readings was not effective in improving diabetes control.

A 6-month randomized control trial utilizing the Livongo for Diabetes RPM program[28] compared with usual care also showed the

ineffectiveness of just lifestyle counselling for high alert values. The Livongo Care Team of certified diabetes educators contact patients for the first uploaded glucose reading of >250 mg/dL and anytime it was >400 mg/dL or <50 mg/dL. They would then provide lifestyle counseling but no medication advice. Baseline HbA1c levels in the Livongo patients, 85% of whom were taking insulin, fell by 1.1% from 10.3% to 9.2%. Baseline HbA1c levels in the usual care patients, 88% of whom were taking insulin, fell by 0.8% from 10.0% to 9.2%. HbA1c levels decreased significantly in both groups but the changes were not statistically different between the 2 groups. The similar results between the RPM and Usual Care groups in the present and Livongo studies suggest that RPM followed only by lifestyle counselling and not by any changes in pharmacological therapy has little effect on improving diabetes control.

Few RPM programs provide ongoing pharmacological therapy for insulin-requiring patients. A number will calculate a preprandial bolus dose of a short- or rapid-acting insulin if the patient provides the estimated carbohydrate content of the meal, the prescribed amount of insulin per gram of carbohydrate and the current glucose level before the meal. These recommended bolus doses require that patients test before each meal and do not provide ongoing glucose patterns that are necessary for changes in insulin doses to subsequently improve diabetes control. Furthermore, the meal content of both fat[29] and protein[29-31] importantly affects postprandial glucose increases. After this information was published, a Consensus Report of the American Diabetes Association commented on the postprandial metabolic effects of mixed meals that insulin dosing decisions "should not be based on carbohydrate counting".[32] Rather, the Expert Panel recommended that glucose patterns before meals should guide decision making.

A few RPM outpatient programs will analyze glucose readings and recommend changes in basal insulin doses based on before breakfast values. However, to our knowledge, only Hygieia™ adjusts insulin doses in basal/bolus insulin regimens as well as basal alone ones. This occurs by patients using their specific meter and removing insulin management from PCCs to be followed in separate endocrinologist-supervised programs. In contrast, not only do PCCs retain insulin management with Insulin Insights,™ this CIDAA program can accept glucose readings from over 60 glucose meters, handle over 20 different insulin preparations (analogue and human) and adjust insulin doses for patients utilizing 10 different insulin regimens (basal insulin alone, bedtime NPH insulin alone, basal/bolus, basal + 1, self mixed/split, premixed [70-75/30-25], premixed [basal/rapid-acting], U-500 regular and the unusual delayed responses to both NPH and U-500 regular insulins).

In addition to recommended insulin dose adjustments by an endocrinologist sent to PCCs, Insulin Insights™ provides 2 other advantages, more frequent interactions with insulin-requiring patients and saving time for PCCs as well as for patients. Two-thirds of patients on insulin fail to achieve the American Diabetes Association's target of <7.0%. Yet a clinical trial showed that if insulin doses were adjusted every 1-4 weeks by an endocrinologist, 88% of patients reached that goal.[33] In addition to more frequent adjustments of insulin doses every 2-3 weeks in the present study, the 9 patients whose insulin doses either did not change or were reduced but still achieved respectable reductions of HbA1c levels suggest that more frequent interactions between PCCs and patients could improve adherence to prescribed insulin doses and possibly a more healthy lifestyle.

In the present study, PCCs spent much less time adjusting insulin doses using Insulin Insights™. Time savings were also tracked in a different manner in a previous pre- post remote glucose monitoring study utilizing Insulin Insights™ in which 28 patients were followed by a nurse practitioner for 3 months and 17 for 6 months and reports also generated every 2-3 weeks.[26] The nurse practitioner took 13.7 hours to evaluate and decide on the insulin dose adjustments recommended in 268 reports. A 15 minute in-person visit for these 268 interactions would have required 67 hours. The use of Insulin Insights™ freed up more time for other patients to be seen. In addition, almost all patients prefer virtual visits for these interactions saving transportation and waiting times.

Remote glucose monitoring programs in which endocrinologists analyze the glucose readings and adjust insulin doses are very effective.[33-35] In 2019, the American Association of Medical Colleges listed 6439 physicians involved in patient care who specialized in Endocrinology/Diabetes/Metabolism.[36] With 7.7 million people receiving insulin, (30%[11] of the known 25.8 million people diagnosed with diabetes), if all of these specialist physicians saw the insulin-requiring patients, there would be 1196 patients per endocrinologist. Most endocrinologists are congregated in or near larger cities and many endocrinologists do not take care of people with diabetes.

The limited number of endocrinologists, especially those caring for people with diabetes, and their geographic distribution, underscore the need for PCCs to undertake insulin dose adjustments in a more effective way. Physicians state that a major factor in their reluctance to start and subsequently intensify insulin treatment is due to time constraints, and for some, inexperience.[12,15,21,22] Because of the number of patients that they are following, time constraints also involve less frequent visits with most patients being routinely seen every 3 months or so which is particularly problematic for insulin-requiring patients. Remote glucose monitoring with endocrinologist-guided insulin dose adjustment recommendations would allow PCCs to reproduce a very effective treatment program for their patients taking insulin.[33]

CONCLUSIONS

Although the RPM program lessened clinical hypoglycemic risk, CIDAAs were required to markedly increase insulin doses effectively and safely in these under-insulinized patients to improve diabetes control more than RPM alone or Usual Care. Utilizing CIDAAs in insulin-requiring patients, whether enrolled in an RPM program or not, would facilitate insulin dosing by PCCs by meeting several challenges. Importantly, it would increase the number of interactions with patients as well as provide appropriate recommendations, probably by an endocrinologist involved in writing the algorithms. As PCCs consider accepting or modifying these recommendations and observe the subsequent glycemic outcomes, the algorithms would also have an additional educational benefit. Improved diabetes control would reduce the possibility of longer-term diabetic complications which would lead to associated cost savings. A possible added benefit in some medical care systems might be the easily available documentation that the reports of Insulin Insights™, would provide for facilitating payments for telehealth encounters.

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