RESEARCH ARTICLE

Use of Computerized Insulin Dose Adjustment Algorithms to Facilitate Adjusting Insulin Doses by Primary Care Providers

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Abstract

Insulin use is challenging for both primary care providers (PCPs) and patients. For PCPs, a major challenge is time constraints, and for many, inexperience. For patients, it is providing enough fingerstick glucose readings for insulin dose adjustments to be made. The first author has developed algorithms for adjusting insulin doses based on the following principles. Depending on when injected, each component of the insulin regimen has a maximal effect on a specific period of the 24-hour cycle, e.g., overnight, morning, afternoon, evening. The glucose pattern in that period determines whether the dose of that component of the insulin regimen requires adjusting or not. There needs to be enough glucose readings in a period that reflects a patient's current lifestyle for a decision to be made about that component of the insulin regimen that maximally affects that period.

A registered nurse using these algorithms at clinic visits lowered HbA1c levels in 111 poorly controlled insulin-requiring patients from 11.0% to 7.2% within 9-12 months. When computerized, these FDA-cleared algorithms produce a report within 15 seconds after glucose meters are downloaded with recommendations for insulin dose adjustments that the PCP can modify or accept. In a pilot project utilizing these computerized algorithms in poorly controlled insulin-requiring patients who performed remote glucose monitoring, baseline HbA1c levels decreased from 10.0% to 8.1% in 3 months and to 7.6% in 6 months without any clinic visits for adjustment of insulin doses. In a proof-of-concept project utilizing these computerized algorithms in poorly controlled insulin-requiring patients using continuous glucose monitoring (CGM), baseline HbA1c levels decreased from 11.5% to 8.3% over a mean of 3 months.

Computerized insulin dose adjustment algorithms and CGM meet both the PCP and patient challenges. These innovations should be strongly considered to effectively decrease HbA1c levels, especially in poorly controlled patients.

Keywords: Insulin therapy, Dose adjustment algorithms, Remote glucose monitoring, Continuous glucose monitoring

1.0 Background

The American Diabetes Association's (ADA) HbA1c goal is <7.0% in most people with diabetes[1] which is achieved by only 50%.[2] Twenty-eight percent of people with diabetes have HbA1c levels of >8.0% while 16% have levels >9.0%.[2] Although all people with type 1 diabetes require insulin, that is not the case for people with type 2 diabetes. Initially, newly diagnosed patients with type 2 diabetes can usually be controlled by one non-insulin drug (usually metformin) but require the subsequent addition of other classes of non-insulin drugs as insulin secretion progressively diminishes.[3] Diet alone, metformin and sulfonylurea therapy[4] do not alter this progressive decrease in insulin secretion, and unfortunately, so far none of the newer classes of drugs seem able to do so either. Eventually, insulin secretion falls to the point where 25-30% of type 2 diabetic patients require insulin.

1.1 Insulin therapy by Primary Care Providers (PCPs)

Ninety percent of people with diabetes are cared for by PCPs[5] who are particularly challenged in using insulin. This is evidenced by; a) the 3-7 years it took to start insulin once people with type 2 diabetes had failed maximal doses of 2 or 3 non-insulin drugs (HbA1c level >8.0%),[6,7] b) the average HbA1c level range of 8.9% to 9.8% with a mean of 9.3% when insulin was started in the United states,[6-10] and 9.8% and 8.4% in the United Kingdom and Germany, respectively,[11] (c) the mean HbA1c level of 9.7% when insulin was intensified in patients failing basal insulin alone,[7,10] (d) the fact that insulin intensification occurred in only 25-30% of patients and its discontinuation in a similar number[10, 12-18] and e) the average HbA1c level range of 7.9% to 9.3% with a mean of 8.5% in patients receiving insulin in the United States[8,19,20] and 8.4%, 8.0%, 7.9%, 7.8% and 7.7% in the United Kingdom, Spain, France, Italy and Germany, respectively.[21]

Risk factors for HbA1c levels >9.0% in 6973 patients at the Cleveland Clinic, a large integrated delivery system, were a long duration of diabetes, infrequent office visits and insulin therapy.[22] No doubt the long duration of diabetes was associated with such low levels of insulin secretion that endogenous insulin therapy was necessary. Only one-quarter of these patients achieved HbA1c levels of <8.0% in one year.[22] Both PCPs and patients face challenges in using insulin. For PCPs, it's the time constraints of a relatively brief visit in which other problems must be addressed as well as obtaining the glucose readings, organizing and analyzing them before making appropriate insulin dose adjustment decisions. For many, it's also a lack of experience in making these dose adjustment decisions, especially in patients using intensive insulin regimens, i.e., 2 or more injections of 2 different insulin preparations. For patients, the biggest challenge is providing enough glucose readings for their PCPs to make appropriate clinical decisions.

1.2 Detailed Treatment Protocols Taught to Mid-Levels

The first author has developed detailed diabetes treatment protocols and taught them to mid-levels (registered nurses, nurse practitioners [NPs], physician assistants [PAs] and clinical pharmacists [CPs]) for nearly 40 years. How to adjust insulin doses for all insulin preparations and combinations is also taught. After being trained, a registered nurse, hired by Los Angeles County, was placed in a Family Medicine Clinic where the PCPs referred their out of control patients to her. She was allowed to use the officially approved treatment protocols and rules for adjusting insulin doses. Over the course of several years, 178 patients were referred to her,[23] 99% of whom

had type 2 diabetes and 65% were females. Their ages and duration of diabetes (years ± SD) were 54.3 ± 7.1 and 11.5 ± 7.1, respectively. Their treatments at referral and 9-12 months later are shown in Table 1. Treatment intensification occurred with insulin started in 40 patients and intensification of the insulin regimen in 79 patients. HbA1c levels at referral fell from 11.1% to 7.2%. Forty-nine percent of these poorly controlled patients at referral met the ADA's HbA1c goal of <7.0%. In the 111 patients who were taking insulin at referral, their HbA1c levels at fell from 11.0% to 7.2%. Even if all of the patients not taking insulin after 9-12 months met the ADA's HbA1c goal of <7.0%, 40% of those receiving insulin did as well (see section 2.0 for comparison).

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Table 1 – **Patient Treatment Modalities**

Drugs	Referral*	Final*
OAD†	67	27
Bedtime NPH Insulin (plus OAD)	44	15
≥2 Injections of Insulin‡	53	132
Premixed Insulin‡	14	4

*Number of patients; †Oral antihyperglycemic drugs (metformin, sulfonylureas, pioglitazone); ‡Human insulin (NPH, regular)

1.3 Computerization of the Rules for Adjusting Insulin Doses

There are 3 basic principles underlying the rules for adjusting insulin doses.

a) Depending on when injected, each component of the insulin regimen has a maximal effect on a specific period of the 24-hour cycle, e.g., overnight, morning, afternoon, evening.
b) The glucose pattern in that period determines whether the dose of that component of the insulin regimen requires adjusting or not.
c) There needs to be enough glucose readings in a period that reflects a patient's current lifestyle for a decision to be made about that component of the insulin regimen that maximally affects that period.

The computerized algorithms following these principles and describing the rules for adjusting insulin doses have been cleared by the FDA in the United States and CE registered in the European Union. They can interact with over 60 glucose meters and with continuous glucose monitors. They can handle all of the over 20 different types of insulin preparations, e.g., short-acting regular insulin, all rapid-acting analogue insulins, intermediate-acting NPH insulin, all basal analogue insulins, all premixed insulins and U-500 regular insulin. The algorithms can analyze 8 different insulin regimens, e.g., basal insulin alone, bedtime NPH insulin alone, basal/bolus, self-mixed/split insulins,

premixed insulins, U-500 regular insulin and the unusual delayed responses to both NPH[24,25] and U-500 regular[26] insulins.

Registering a patient to use the computerized insulin dose adjustment algorithms is simple and straightforward. After the initial registration of the patient into the system requiring date of birth, height, weight, sex, insulin regimen, approximate time range for each meal and bedtime and pre- and post-prandial targets selected by the clinician, there is no further administrative interactions. Within 15 seconds of downloading a glucose meter at a visit into the program containing the computerized insulin dose adjustment algorithms (called Insulin Insights), a report is generated that includes a Day View consisting of the date, time and glucose reading of all values, a scatterplot of these readings, the glucose readings organized into before and after each meal and before bedtime, an analysis of the glucose values and recommendations for insulin dose adjustments (if necessary) that the clinician can accept or modify. The Day View is supplied in case there are identified glucose values that do not reflect the patient's usual lifestyle, e.g., missed insulin dose(s) or missed or late meals, short steroid treatment for exacerbation of pulmonary disease, etc. These values can be deleted before the analysis takes place. Once the clinician designates the new doses, these serve as the basis for the subsequent report.

The report generated by Insulin Insights in less than a minute certainly meets the visit time constraints of PCPs. It also provides guidance for adjusting insulin doses by an experienced endocrinologist and could serve as ongoing educational material for less experienced PCPs.

2.0 Remote Glucose Monitoring (RGM)

PCPs also face scheduling time constraints for adjusting insulin doses. Patients with diabetes are routinely seen only every 3 months or so in busy primary care practices. This is particularly problematic for those requiring insulin. Two-thirds of patients on insulin fail to achieve the ADA goal of <7.0%.[27] Yet a clinical trial showed that if insulin doses were adjusted (by an endocrinologist or certified diabetes educators under approved protocols) every 1-4 weeks, 88% of patients reached that goal.[27] Remote glucose monitoring in which glucose readings are transmitted to the patient's PCP in a format that facilitates insulin dose adjustments has the great potential of increasing the frequency of interactions between the two as well as saving time for both. Remote glucose monitoring has taken on even greater potential importance during the Covid-19 pandemic as in many places patients are being managed by telemedicine, the use of which is likely to persist after the pandemic subsides.

2.1 Utilizing Insulin Insights for RGM[28]

A pilot project was carried out to evaluate the use of Insulin Insights for remote glucose monitoring in a challenging population of poorly controlled, under-resourced, minority, insulin-requiring patients served by a Los Angeles community clinic. Several glucose meters are available that if attached to a smartphone can send their glucose readings when measured to the meter company's secure, Health Insurance Portability and Accountability Act (HIPAA) - approved cloud. At stated intervals, Insulin Insights can access these glucose readings stored on the cloud, generate the report described above (absence the Day View) and send it to the patient's PCP.

2.2 RGM Pilot Project Methods

Adult patients eligible for the study had been taking insulin for at least 6 months with an HbA1c level within the past month of ≥8.0% and used a smartphone. They were given an

iHealth Align glucose meter with an associated mobile application available from the Web that attached to a smartphone. The mobile application automatically transmitted each glucose reading to the account of the user in the iHealth cloud system. Mellitus Health's server was notified each time that there was a new reading for that patient. Two to 3 weeks after the last contact with the patient by the clinic's staff person (which is also noted by the Mellitus Health server), the server requested the glucose values (along with the date and time that they were measured) from the iHealth server that had been obtained since the last report was generated. This new report, was received electronically by the staff person, printed and shown to an assigned NP who decided if any insulin dose adjustments were necessary. She then had the staff person contact the patient with either any new doses or maintenance of the previous ones after ascertaining that the patient had been taking the previously prescribed insulin doses. If the NP had raised any questions about unusual glucose values, the staff person inquired about the circumstances surrounding them and fed that information back to the NP before confirming any new insulin doses. HbA1c levels were measured 3 and 6 months after enrollment.

2.3 RGM Pilot Project Results

Forty-seven patients were enrolled but 19 patients were dropped from the study before 3 months for the following reasons: 9 consistently measured too few times for dose adjustment decisions to be made; 6 could not be reliably reached; 2 continued not to take their recommended insulin doses; and 2 were unable to consistently use the smartphone/meter combination. The remaining 28 were 55.9 ±8.6 (SD) years old, 15 were female, 20 were Hispanic, 4 were non-Hispanic Black, 3 were White and 1 was Asian, 11 were on a basal alone insulin regimen, 14 on a basal/bolus one and 3 on a self-mixed/split one. Eleven more patients were dropped between 3 and 6 months for the following reasons: 7 consistently measured too few times for dose adjustment decisions to be made; 2 could not be reliably reached; and 2 continued not to take their recommended insulin doses.

The baseline HbA1c (±SD) levels of the 28 patients of 10.0% ±1.2 fell 1.9% to 8.1% ±1.0 at 3 months and another 0.5% to 7.6% ±0.8 at 6 months, P $<10^{-6}$ (Figure 1). Thirty-six percent of the patients achieved an $HbA1_c$ level of <7.5% and 50% of <8.0%. After the initial education visit to learn how to use the smartphone/meter system, there were no clinic visits for adjustment of insulin doses.

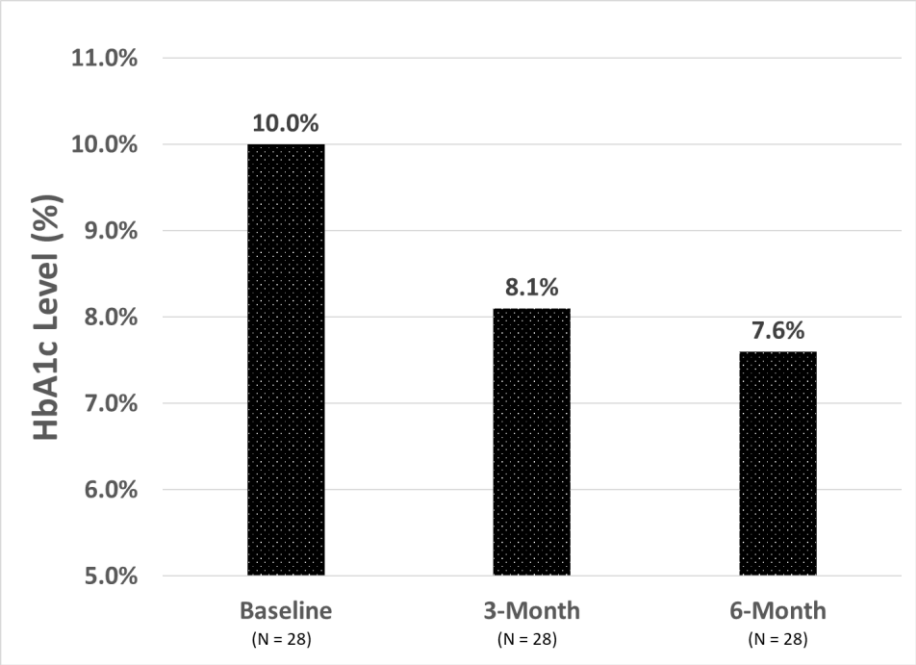

Figure 1 – *Effect of Computerized Insulin Dose Adjustment Algorithms Analysis of Remote Glucose Monitoring*

2.4 RGM Pilot Project Conclusions

Remote glucose monitoring utilizing these computerized insulin dose adjustment algorithms: a) saved a lot of time for both patients and PCPs; b) provided experience-tested insulin dosing recommendations (which can be modified or accepted); c) increased PCP-patient interactions; and d) markedly lowered HbA1c levels in this challenging, poorly controlled, insulin-requiring population. However, for billing purposes in fee-for-service medical care systems, the NP will need to have some direct contact with the patient.

3.0 Continuous Glucose Monitoring (CGM)

A large challenge for patients who use insulin is to provide enough fingerstick glucose readings to allow clinicians to make insulin dose adjustments. The pilot project described above to evaluate the use of Insulin Insights for remote glucose monitoring illustrates this challenge. Of the 48 enrolled patients, 16 or one-third had to be dropped from the project because they did not provide enough readings for adjustment decisions. This was in spite of agreeing to test before breakfast in those taking a basal insulin alone or a minimum of twice a day for those on an intensified insulin regimen, i.e., 2 or more injections of 2 different insulin preparations.

CGM easily meets this patient challenge. A glucose sensor that provides glucose readings every 5 (Medtronic, Dexcom) or 15 (Abbot) minutes is inserted by the patient subcutaneously. The Medtronic sensor needs to be changed every 6 days, the Dexcom one can last up to 3 months and the Abbot ones need to be changed every 10-14 days. Most CGM is done by patients with type 1 diabetes but the Abbott CGM is starting to be used by some with type 2 diabetes. Currently, CGM is mostly used in patients followed by endocrinologists. Few PCPs have the experience to analyze the more complex data output of CGM and decide on insulin dose adjustments.

3.1 Utilizing Insulin Insights for CGM[29]

To circumvent this PCP issue, a proof-of-concept project was carried out to determine if Insulin Insights could handle the many more glucose readings of CGM compared to the many fewer ones produced by fingersticks. In a San Diego community clinic that serves a minority, under-resourced population, poorly controlled patients with diabetes (HbA1c levels >9.0%) are often referred to a CP specially trained in diabetes care. She routinely uses Insulin Insights in patients taking insulin and performing fingerstick glucose tests.

3.2 CGM Proof-of-Concept Project Methods

For this project, the pharmacy purchased 13 CGMs (Free Style Libre Pro) which were given to the first 13 insulin-requiring patients at referral who agreed to be seen every 2 weeks. The CP transferred the CGM glucose readings (date, time, values) to a secure, HIPAA-approved cloud on which Insulin Insights resided. Within 15 seconds of transferring the CGM readings, the CP received the report described above. The primary outcome was change in HbA1c levels from baseline. Secondary outcomes were time in ranges (TIRs) for glucose concentrations of <54 mg/dl (level 2 hypoglycemia), 54-69 mg/dl (level 1 hypoglycemia), 70-180 mg/dl (target range), 181–250 mg/dl and ≥250 mg/dl.

3.3 CGM Proof-of-Concept Project Results

Ten of the 13 patients (7 females) were on basal insulin alone and 3 were on basal/bolus regimens. Twelve had type 2 diabetes and 1 had type 1 diabetes. Mean (±SD) ages were 52.7 ±9.2 years and mean BMIs were 31.6 ±7.8. Reports were generated at each visit. The mean number of CGM reports was 4.7 per patient covering a mean period of 97 days or one every 3 weeks. Glycemic responses are shown in Table 2. HbA1c levels (±SD) markedly fell from 11.5 ±1.4 to 8.3 ±0.9%. Time spent with glucose concentrations >250 mg/dl decreased from 44% to 23% with a concomitant increase in time in the target range of 70-180 mg/dl from 29% to 51%. There were no significant differences in time spent at hypoglycemia levels 1 or 2 nor any episodes of severe hypoglycemia (assistance required for treatment). As can be appreciated in Figure 2, the pattern of glycemia shifted downward so that there was significantly less time spent with glucose concentrations >250 mg/dl and significantly more time with glucose concentrations in the target range of 70-180 mg/dl with no difference between 181-250 mg/dl. The total daily baseline dose of insulin was 47 units which increased to 67 units, a 42% rise. Since insulin regimens were not changed, the increase was simply due to raising insulin doses.

Table 2 - Glycemic Responses

	Initial Report	**Final Report**	**P Value**
Time in Range (% ±SD)			
<55 mg/dl	0.2 ±0.7	O.6 ±1.4	0.32
55 – 69 mg/dl	0.5 ±1.3	1.6 ±2.3	0.15
70 – 180 mg/dl	28.8 ±27.2	50.6 ±24.9	0.01
181-250 mg/dl	26.3 ±11.0	24.2 ±10.5	0.58
>250 mg/dl	44.2 ±25.0	22.9 ±17.7	0.01
HbA1c Level (% ±SD)			
	11.5 ±1.4	8.3 ±0.9	$<10^{-6}$

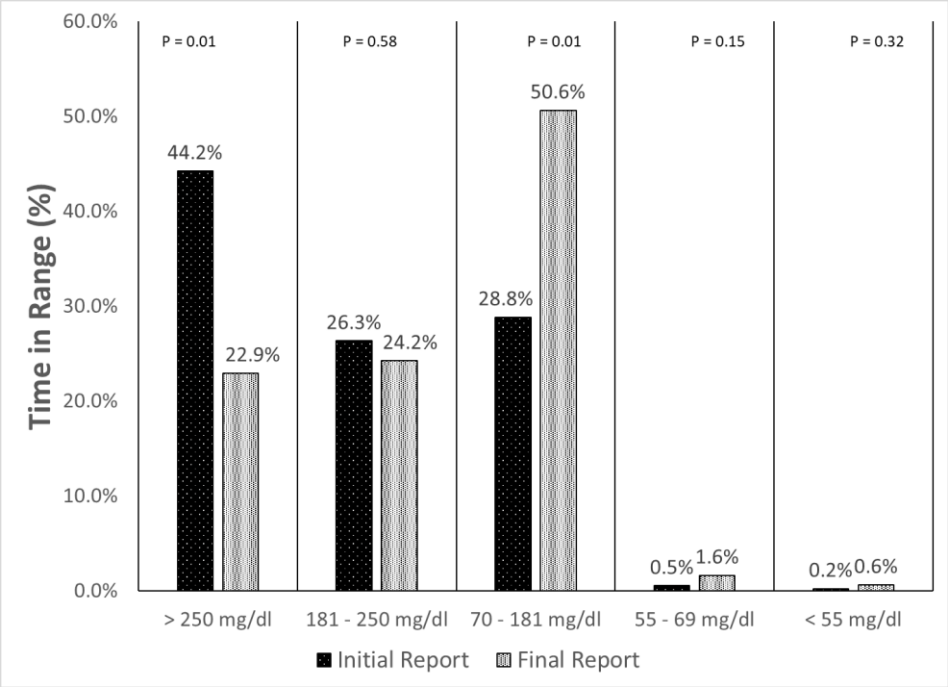

Figure 2 – *Effect of Computerized Insulin Dose Adjustment Algorithms Analysis of Continuous Glucose Monitoring*

3.4 CGM Proof-of-Concept Project Conclusions

Increasing time in the target range is associated with a beneficial effect on diabetic retinopathy.[30] Combining CGM with computerized insulin dose adjustment algorithms meets 2 of the biggest challenges of controlling diabetes in insulin-requiring patients, namely, providing enough glucose readings by patients and time constraints for PCPs. Utilizing these 2 innovations together, especially if the glucose monitoring results can be provided remotely and therefore more frequently, should improve diabetes control with subsequent beneficial effects on diabetes complications and resultant lowering of health care costs.

4.0 Final Conclusions

Although the microvascular complications of diabetes can be devastating, they can be avoided. The landmark Diabetes Control and Complications Trial (DCCT)[31] in patients with type 1 diabetes and both the Kumamoto Study[32] and United Kingdom Prospective Diabetes Studies (UKPDS)[33] in patients with type 2 diabetes proved that these complications were caused by ongoing hyperglycemia. The DCCT demonstrated that if HbA1c levels could be kept below 7.0%, the relative risk of the development or progression of the microvascular complications was extremely low. The risk increased somewhat with values between 7.0% and 8.0% but rose exponentially over 8.0%.[34] A 1.0% decrease in HbA1c levels was associated with 35-40% less microvascular complications.[31,35] The direct medical costs of diabetes care in the United States in 2017 was 237 billion dollars, a sizeable proportion of which was related to the microvascular complications.[36] The clinically beneficial effects of a 1.0% drop in HbA1c levels are also associated with a reduction of $556 to $1993 per patient per year in medical care charges, depending on the presence of cardiovascular disease and/or hypertension. These savings noted in 1997[37] were adjusted by the yearly consumer price index (CPI) to 2014. Since the rate of increase of medical care costs is more than the CPI, the yearly savings are likely higher. Given the poor control under current approaches in insulin-requiring patients, innovations, including the ones described in this review, should be strongly considered.

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