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ORIGINAL ARTICLES

Use of Continuous Glucose Monitoring to Estimate Insulin Requirements in Patients with Type 1 Diabetes Mellitus During a Short Course of Prednisone

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Abstract

Background:

Insulin requirements to maintain normoglycemia during glucocorticoid therapy and stress are often difficult to estimate. To simulate insulin resistance during stress, adults with type 1 diabetes mellitus (T1DM) were given a three-day course of prednisone.

Methods:

Ten patients (7 women, 3 men) using continuous subcutaneous insulin infusion pumps wore the Medtronic Minimed CGMS® (Northridge, CA) device. Mean (standard deviation) age was 43.1 (14.9) years, body mass index 23.9 (4.7) kg/m^2, hemoglobin A1c 6.8% (1.2%), and duration of diabetes 18.7 (10.8) years. Each patient wore the CGMS for one baseline day (day 1), followed by three days of self-administered prednisone (60 mg/dl; days 2–4), and one post-prednisone day (day 5).

Results:

Analysis using Wilcoxon signed rank test (values are median [25th percentile, 75th percentile]) indicated a significant difference between day 1 and the mean of days on prednisone (days 2–4) for average glucose level (110.0 [81.0, 158.0] mg/dl vs 149.2 [137.7, 168.0] mg/dl; p = .022), area under the glucose curve and above the upper limit of 180 mg/dl per day (0.5 [0, 8.0] mg/dl·d vs 14.0 [7.7, 24.7] mg/dl·d; p = .002), and total daily insulin dose (TDI) , (0.5 [0.4, 0.6] U/kg·d vs 0.9 [0.8, 1.0] U/kg·d; p = .002). In addition, the TDI was significantly different for day 1 vs day 5 (0.5 [0.4, 0.6] U/kg·d vs 0.6 [0.5, 0.8] U/kg·d; p = .002). Basal rates and insulin boluses were increased by an average of 69% (range: 30–100%) six hours after the first prednisone dose and returned to baseline amounts on the evening of day 4.

Conclusions:

For adults with T1DM, insulin requirements during prednisone induced insulin resistance may need to be increased by 70% or more to normalize blood glucose levels.

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (GAA_{180}) glucose area above the upper limit of 180 mg/dl, (G_{ave}) average glucose per day, (TDI) total daily insulin dose, (STAI) State-Trait Anxiety Inventory, (SD) standard deviation, (T1DM) type 1 diabetes mellitus

Keywords: continuous glucose monitoring, insulin requirements, prednisone, stress, type 1 diabetes mellitus

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Introduction

The focus in management of type 1 diabetes mellitus (T1DM) is to normalize blood glucose levels and reduce glucose variability in order to minimize or eliminate diabetic complications, such as retinopathy, nephropathy, and neuropathy. Therapy is optimized by administering exogenous insulin in a way that matches physiologic needs. This requires either continuous glucose monitoring or at least 8–10 self-administered blood glucose determinations (finger sticks) each day and a flexible regimen of insulin delivery.[1] The regimen for insulin administration requires multiple daily injections or continuous subcutaneous infusion with approximately 50% of the total daily insulin dose (TDI) as basal insulin and approximately 50% as prandial insulin.[2]

Effective management of diabetes must take into consideration physical, psychological, and hormonal stressors, which affect the need for insulin.[3] During stress, levels of cortisol, catecholamines, and growth hormone increase, which lead to an increase in hepatic glucose production, lipolysis, and insulin resistance for both diabetic and nondiabetic individuals[4,5] For patients with T1DM, daily insulin requirements may need to be adjusted to compensate for stress.[6] Some are sensitive to stress and require increased insulin doses, while others are not and do not have increased insulin requirements. The difficulty in calculating such adjustments often results in poor blood glucose control.[7] The TDI may increase with the degree of stress response (mild, moderate, or severe). The following formula has been used to estimate total daily insulin requirements:

TDI (U/day) = Weight (kg) * a "constant"

where the "constant" is 0.6 for baseline conditions for the moderately active or sedentary adult, 0.7–0.8 for mild stress, 0.8–1.0 for moderate stress, 1.0–2.0 for severe stress, and more than 2.0 U/kg per day for life threatening stress or ketoacidosis.[2,8,9]

Synthetic corticosteroids, such as prednisone, are used to reduce inflammation in a variety of disorders. They are used chronically for conditions such as Addison's disease and bronchial asthma and episodically for conditions such as dermatitis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosis, and allergic reactions. For biologic activity, prednisone relies on conversion to prednisolone by 11β-hydroxysteroid dehydrogenase type 1.[10] When taken orally, prednisone has similar anti-inflammatory and immunosuppressive properties as cortisol but is four times more potent.[11] The biologic half-life of prednisone is 12–36 hours, but its duration of action is variable depending on the individual and the continued intracellular glucocorticoid action even after removal from the circulation.

The effect on carbohydrate and lipid metabolism mimics the natural hormonal response by increasing hepatic glycogen deposition, gluconeogenesis, peripheral insulin resistance, free fatty acid production, and the permissive actions of catecholamines and glucagon. The overall result is a protection of glucose-dependent organs, (i.e. the brain and heart), and an exacerbation of the diabetic state. The purpose of this study was to determine the amount of insulin required by patients with T1DM during a three-day course of prednisone. The data from this study will be used clinically to recommend insulin doses when prednisone is prescribed in patients with T1DM.

Patients and Methods

Ten patients (7 women, 3 men) using continuous subcutaneous insulin infusion (CSII) pumps were recruited for this study. Patients were eligible to participate if they had T1DM without major complications related to diabetes and were using CSII therapy. Each patient signed an informed and witnessed consent form approved by the Cottage Health Systems Internal Review Board. The patients were trained in the use and calibration techniques of the CGMS® device (Medtronic MiniMed, Inc., Northridge, CA). All patients used the OneTouch® UltraSmart® blood glucose meter (LifeScan, Inc., Milpitas, CA) as their self-monitored blood glucose meter and entered at least 4 blood glucose values per day into the CGMS. The CGMS is an approved ambulatory subcutaneous continuous glucose monitor based on glucose oxidase, which records approximately 288 glucose measurements from interstitial fluid per 24-hour period. Blood glucose values from the CGMS are stored in the device for download and are not available in real-time.

The mean [standard deviation (SD)] age of the patients was 43.1 (14.9) years, the body mass index was 23.9 (4.7) kg/m^2, the hemoglobin A1c was 6.8 (1.2)%, and the duration of diabetes was 18.7 (10.8) years. **Table 1** gives a summary of the characteristics of the ten patients who participated in the study. Prior to the current study, the

Table 1.
Patient Characteristics

Patient ID	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Ave. Insulin (U/day)	Initial HbA1c (%)	Duration of diabetes (yrs)
02	24	169.0	103.0	35.9	42.5	8.9	20
03	47	156.2	57.7	23.6	28.6	5.9	23
04	44	188.0	90.0	25.4	44.1	5.4	28
05	62	182.0	69.9	21.2	22.9	6.4	1
09	32	165.1	57.3	21.0	46.7	6.3	15
10	65	169.5	55.3	19.2	33.4	5.9	39
12	30	171.0	71.4	24.2	41.4	7.9	10
13	31	170.2	75.0	25.8	36.5	6.2	12
14	36	175.0	68.9	22.4	40.0	8.3	13
17	60	169.0	58.8	20.6	25.8	6.6	26

patients wore continuous glucose monitors (CGMS) to optimize basal insulin infusion rates.[12] Optimization involves wearing the CGMS and skipping one meal each day. Basal insulin infusion rates are then evaluated and adjusted without the interference of meals and bolus insulin. Basal infusion rates are verified with additional monitoring and skipping meals.

After basal insulin rates were optimized (glycemia sustained in the range of 70-120 mg/dl in the fasting and pre-meal time periods), the patients wore the CGMS for one baseline day (day 1) and then took 60 mg of prednisone with breakfast for each of the following three days (days 2–4). Patients were followed with the CGMS for at least one day (day 5) following the last day of prednisone. Based on data from the first patient, it was obvious that the sensitivity to insulin dropped within hours of the first dose of prednisone. Thus, we prospectively increased the total daily dose of insulin (basal infusion rates and boluses) for all subsequent patients by 30–50% six hours after the first dose of prednisone and returned it to a normal level in the evening of day 4. During prednisone days, the patients would call or email Sansum Diabetes Research Institute with their self-monitored blood glucose values from the previous day and insulin doses were then adjusted. The same physician monitored the patients for the entire study.

Since the CGMS sensors are approved for only 72 hours, patients were sent home with an extra sensor for insertion after three days. Patients kept detailed food and exercise diaries before, during, and after the prednisone days. Information from the glucose meter and CSII pump were downloaded at the end of the test period. To monitor daily emotional stress levels, patients completed the State-Trait Anxiety Inventory (STAI)[13] which consists of a trait portion and a state portion. Both parts were completed at the beginning of the trial, and the state portion of the questionnaire was completed at the same time each day during the test period.

Statistics

Data were analyzed with SigmaStat and SigmaPlot (Systat Software, Inc., San Jose, CA). Significance was determined at the 0.05 level.

Results

Data were monitored for completeness. All patients were supplied with the same type of meter and given specific instructions for continuous blood glucose self-monitoring and entering of values into the CGMS. Not all ten patients were able to continue past 5 days; for the patients who did continue with the CGMS, blood glucose levels were normalized by days 6 and 7. Only days completed by all ten patients—day 1 before prednisone, days 2–4 during prednisone, and day 5 without prednisone—were used for analysis. Medtronic MiniMed Solutions software version 3.0b was used to calculate the glucose average [(G_{ave}) in mg/dl] for each day and the area under the glucose curve above the upper limit of 180 mg/dl [(GAA_{180}) in mg/dl·d]. Representative tracings from one patient are shown in **Figure 1**. No changes in diet or activity were seen in any patient during the study period.

One-way repeated measures of analysis showed no significant difference among days 2–4 for total insulin use per kilogram per day, for G_{ave} each day, and for GAA_{180}. Values for days 2–4 were combined and the mean used for analysis.

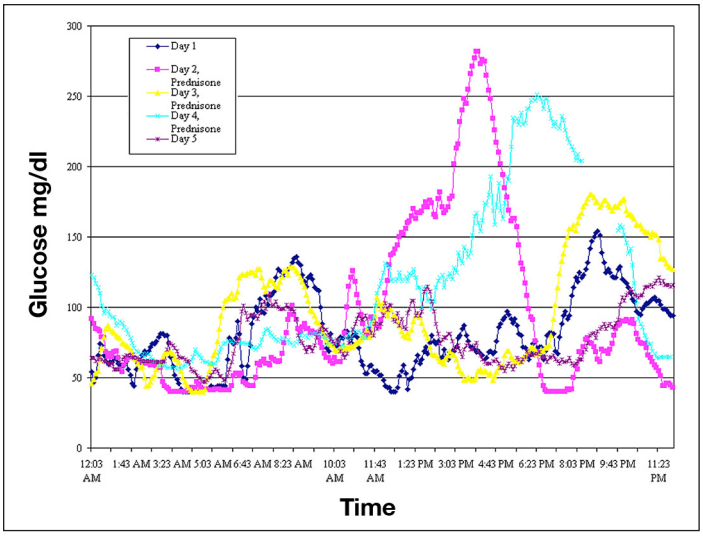

Figure 1. Representative CGMS® tracings from one patient with and without prednisone. Insulin doses: Day 1, 0.49 U/kg (no prednisone); Day 2, 1.09 U/kg, Day 3, 0.89 U/kg, and Day 4, 1.00 U/kg (on prednisone); Day 5, 0.86 U/kg (no prednisone).

With the Wilcoxon signed rank test, a significant difference between day 1 and the mean of days on prednisone (days 2–4) was seen for G_{ave} (p = .022), GAA_{180} (p = .002), and TDI (p = .002). Results are shown in **Table 2**. TDI was also significantly different for day 1 versus day 5 (p = .002) indicating that insulin requirements were still above normal one day after prednisone was stopped. **Figure 2** shows Tukey's box plots of the median, interquartile ranges, and 5th and 95th percentiles for G_{ave} (**Figure 2A**), the GAA_{180} (**Figure 2B**), and TDI (**Figure 2C**).

The mean (range) for day 1, day 2–4, and day 5 for G_{ave} were 119.1 (60.0–176.0) mg/dl, 153.7 (100.7–221.3) mg/dl, and 139.2 (78.0–192.0) mg/dl, respectively; for GAA_{180} they were 5.8 (0–27.0) mg/dl·d, 20.8 (3.0–63.7) mg/dl·d, and 13.6 (0–40.0) mg/dl·d, respectively; for TDI they were 0.5 (0.3–0.8) U/kg·d, 0.9 (0.5–1.2) U/kg·d, and 0.7 (0.5–0.9) U/kg·d, respectively. Finally, the mean ± SD increase in insulin was 68.9 ± 28.9% and **Table 3** gives the mean percentage increase in insulin for each patient.

The results of the STAI questionnaires showed no difference between the days for psychological and emotional stress. Raw scores [mean SD] for days 1, 2, 3, 4, and 5 were, 34.5 (11.7), 37.3 (14.3), 37.3 (13.1), 39.7 (16.6), and 35.3 (8.6), respectively. Standard scores for days 1, 2, 3, 4, and 5 were, 52.5 (16.9), 52.0 (12.6), 52.4 (13.2), 54.1 (14.9), and 50.3 (7.9), respectively. The STAI records indicated that the patients did not feel anxiety or stress during the time on prednisone; however, there was some irritation with increased blood glucose levels.

Table 2.
Differences Between Day 1, Mean of Days 2–4 on Prednisone, and Day 5 for Glucose Average, Glucose Area Above the Upper Limit (180 mg/dl), and Daily Total Insulin

	Day 1	Mean Days 2–4 on prednisone	Day 5
Glucose average mg/dl/day	110.0 (81.0, 158.0)	149.2 (137.7, 168.0)[b]	141.5 (121.0, 157.0)
Glucose area above upper limit (180mg/dl) mg/dl·day	0.5 (0.0, 8.0)	14.0 (7.7, 24.7)[a]	11.0 (6.0, 21.0)
Total insulin U/kg·day	0.5 (0.4, 0.6)	0.9 (0.8, 1.0)[a]	0.6 (0.6, 0.8)[c,d]

Values are median (25%, 75%).
Differences are Day 1 vs Mean of Days 2–4, [a]p=.002, [b]p=.02.
Differences are Mean of Days 2–4 vs Day 5, [c]p=.01.
Differences are Day 1 vs Day 5, [d]p=.002.

Table 3.
Increase in Insulin During Prednisone Therapy

Patient ID	Insulin Avg. Day 2–4 U/day	Increase (%)
02	62.0	46
03	55.7	95
04	89.4	102
05	36.1	58
09	66.0	41
10	43.8	31
12	56.9	38
13	71.1	95
14	72.5	81
17	52.2	102

There were no instances of hypoglycemia in any patient, and the blood glucose levels remained elevated during the entire course of prednisone. We were in daily contact with each patient and no serious adverse events were noted. The treatment period of three days was insufficient to elicit serious side effects; however, blood pressure was not monitored.

Discussion

Stress has been described by Cannon[4] as a complex change in several physiological systems that prepare a person for "fight or flight." Selye was more interested in adaptation to chronic stress and did much to bring the

concept of "stress" and its effects on the body to the attention of the biomedical community.[5] All definitions of stress involve some disturbance in homeostasis that results in physiological and behavioral responses meant to restore homeostasis. Stress is a multifactorial concept with complex feedback and control loops.[14] During stress, the hypothalamic-pituitary-adrenal and sympathetic-adrenal axes are activated. Physical and hormonal stressors are well-documented stimuli of insulin-antagonist hormones. The levels of cortisol, catecholamines, and growth hormone increase in the body, which lead to an increase in hepatic glucose release, lipid metabolism, and insulin resistance.

In the current study, prednisone, a synthetic corticosteroid, was administered to patients with T1DM to roughly mimic the natural hormonal response to acute stress and to induce insulin resistance. The genomic effects are mediated by glucocorticoids binding to specific receptor proteins in target tissues and directing the production or inhibition of proteins. Thus, most effects of glucocorticoids may not be seen for several hours. In a study by Zarkovic *et al*.[15], increased insulin resistance from glucocorticoid infusion was seen four hours after the start of the infusion. A euglycemic hyperinsulinemic clamp was used to determine insulin sensitivity.

The long-term effects of increased endogenous corticosteroids or chronic corticosteroid therapy are well known[16] and for patients with diabetes the effects on insulin sensitivity are of more concern. Glucocorticoid administration in the intensive care unit of a hospital is beneficial to some patients but harmful to others.[17] Glucocorticoid administration can cause insulin resistance, muscle catabolism, hyperglycemia, impaired immune function, critical-care neuropathy, and poor wound-healing. Thus, glucocorticoids must be administered carefully and patients should be monitored for adverse effects. Intensive insulin therapy has also been advocated in critical care units for certain patients.[18] As with glucocorticoid administration, there are concerns with intensive insulin therapy and patients must be selected with care, based on the nature of their illness and environmental and genetic factors.[19]

Patients in the current study had optimized basal insulin infusion rates[12] prior to starting the three-day course of prednisone. They kept detailed diet and activity records and did not change their diet or activity during the study. We found that increases in insulin doses, both basal infusion rates and boluses, were evident by six hours after the first dose of prednisone. It was clearly too late to wait until blood glucose levels rose and the drug was absorbed. Even when the basal and bolus insulin doses were increased by 30–100% of the usual dose, these increased doses were insufficient to completely counteract

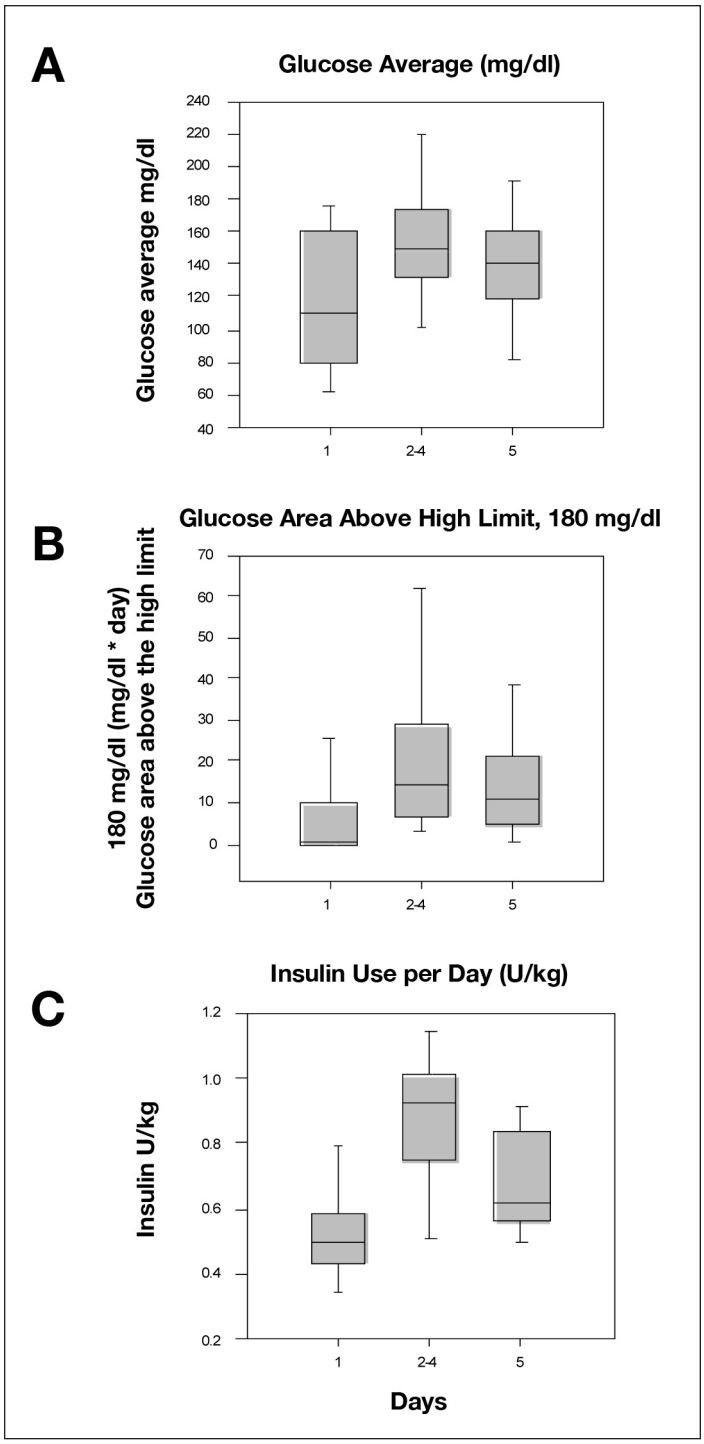

Figure 2. (A) Box plot of median, interquartile range, and 5th and 95th percentiles for glucose average mg/dl: Day 1 vs mean Days 2–4 significantly different (p = .002). **(B)** Box plot of median, interquartile range, and the 5th and 95th percentiles for glucose area above the upper limit, 180 mg/dl: Day 1 vs mean Days 2–4 significantly different (p = .002). **(C)** Box plot of median, interquartile range, and 5th and 95th percentiles for total Insulin U/kg per day: Day 1 vs mean Days 2–4 significantly different (p = .002); Days 2–4 vs Day 5 significantly different (p = .010); Day 1 vs Day 5 significantly different (p = .003).

the increases in blood glucose and insulin resistance. Of note, four patients with the lowest glucose averages and the smallest areas above the upper limit (180 mg/dl) were able to better control their blood glucose levels with frequent glucose monitoring and constant adjustment of their insulin doses. However, complete normalization of blood glucose levels was not achieved. The mean increase for all patients was 68.9 ± 28.9% above usual insulin doses. A future study might involve using real-time continuous glucose monitors for better adjustment of daily insulin doses during prednisone therapy and a comparison of the first 12 hours of prednisone with the last 12 hours on the third day of treatment.

Conclusion

The goal of this study was to estimate the amount of insulin needed to treat patients with T1DM during a short course of prednisone. Administration of oral prednisone for three days did increase blood glucose levels significantly above baseline for the daily glucose average and the glucose area above the upper limit, as shown by continuous glucose monitoring. Increasing the TDIs by 30–100% did not achieve normoglycemia because the additional insulin was given after the blood glucose levels were on the rise. In conclusion, insulin doses should be increased by at least 30% when the corticosteroid therapy is started and may need to be increased by 70% or more to normalize blood glucose levels. The increased insulin administered above the 30% increase needs to be individualized and based on frequently monitored blood glucose levels, but the initiation of at least a 30% increase in insulin dosage at start of therapy is a safe starting dose.

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Disclosure:

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