An eBook on Diabetes

Chapter 1

An Effective Method for Adjusting Insulin Doses

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1. Background

In type 2 diabetes, insulin secretion is depressed approximately 50% at the time of diagnosis and progressively decreases [1] regardless of treatment [2]. Because of this, non-insulin therapies eventually fail in many patients and insulin treatment becomes necessary. Thirty percent of Caucasians and African-Americans and 22% of Latinos are taking insulin (this includes the 5% of type 1 diabetic patients, all of whom require insulin, as well) [3]. Ninety percent of diabetic patients in the United States are cared for by primary care providers (PCPs), usually physicians but also nurse practitioners and physician assistants [4]. However, PCPs are challenged in using insulin. This is evidenced by; a) the median of 7 years it took to start insulin once type 2 diabetic patients had failed maximal doses of 2 or 3 non-insulin drugs (HbA1c level >8.0%) [5,6], b) the average HbA1c level range of 8.9% to 9.8% with a mean of 9.3% when insulin was started [5-9], (c) the mean HbA1C level of 9.7% when insulin was intensified in patients failing basal insulin alone (9), (d) the fact that insulin intensification occurred in only 25-30% of patients and its discontinuation in a similar number [9-16] and e) the average HbA1c level range of 7.9% to 9.3% with a mean of 8.5% in patients receiving insulin [7,17,18].

In one report, one-third of physicians regarded insulin as a treatment of last resort and withheld it until it was “absolutely necessary” [11]. Although most PCPs recognize the effectiveness of insulin, they still regard the initiation of insulin therapy as one of the most difficult aspects of managing patients with type 2 diabetes [19]. The reasons stated for their reluctance to start or intensify insulin included lack of time and experience [20]. This chapter will describe a straightforward, safe and effective method for adjusting insulin doses. It will conclude by describing a tool that will markedly reduce the time challenges faced by PCPs and

facilitate their insulin dose adjustments.

2. General Principles

There is no one correct way to adjust insulin doses but there are certain principles and relationships that underlie an effective approach. These are:

1. Meal patterns

a) The insulin regimen should be placed around the patient's usual meal pattern instead of prescribing an insulin regimen that requires the patient to change the meal pattern to accommodate the regimen. It is difficult for patients to change their patterns of eating.

a) Carbohydrate (CHO) counting as the sole means of determining pre-prandial insulin doses is no longer recommended by the American Diabetes Association (ADA) because of the large effects of the protein and lipid contents of the meal on postprandial glycaemia [21-23]. Rather "self-monitoring of blood glucose (SMBG) should guide decision making" [24]. If CHO counting is used to calculate premeal insulin doses, the dose is based on insulin/glucose ratios and changes in these doses has to occur by changing the ratios.

c) Patients should eat as consistently as possible in regards to timing of meals and content of CHO, protein and fat in each meal. All meals do not need to contain consistent CHO, protein and fat but breakfasts, lunches and supper should each be internally consistent. This is not to say that improvement in nutrition should not be encouraged but insulin dose adjustments need to be made in light of what the patient is actually eating.

2. Variable insulin responses

The response to the same dose of insulin varies by 20-30% from day-to-day in the same patient [25,26].

3. SMBG

a) Preprandial SMBG is much more convenient for patients than postprandial testing and is usually all that is necessary. An exception is when preprandial glucose values are at target but Hb1c levels are over target. In that case, postprandial glucose concentrations may be high even though values return to glucose targets before the next meal. In this situation, postprandial SMBG should be substituted for preprandial SMBG, e.g., instead of testing before lunch, SMBG should occur between 1-2 hours after breakfast.

b) Patients taking a basal insulin alone or bedtime NPH insulin alone need only test before breakfast. For those taking 2 or more injections that include a short- or rapid-acting insulin (intensified regimen), testing before each meal and at bedtime would be ideal but is unrealistic

for most patients. Testing twice a day alternating between meals and bedtime, e.g., before breakfast and supper one day and before lunch and bedtime the second day, will furnish enough information to adjust insulin doses in intensified regimens (although take twice as long compared to testing four times a day).

4. Pattern analysis

Because of the variability in patients' eating schedules and meal contents and in their responses to insulin, adjustment of insulin doses should be made based on SMBG values over a period of time that reflects their usual current lifestyle. Initial titration can utilize glucose values every 3-7 days but once more stable doses are reached, adjustments should occur over weeks to several months. The glucose readings must reflect consistent insulin dosing for adjustments based on the glucose patterns to be valid.

5. Relationships between components of the insulin regimen and their maximal effects during different periods during the day/night

These relationships are critical for the straightforward, effective approach for adjusting insulin doses. The 24 hours of each day/night is divided into 4 periods; morning, afternoon, evening and overnight. There are 5 classes of insulins; a) short-acting, b) rapid-acting, c) intermediate-acting, d) basal, and e) premixed. Depending on when they are injected, each component of the insulin regimen will have its maximal effect during one of the 4 periods described above. The relationship between the class of insulin, when it is injected, what period that reflects its maximal action and which SMBG values measure the glycemia of that period is shown in **Table 1**.

Table 1: Relationships Among Components of Various Insulin Regimens, Times of Injection, Periods of Maximal Effects and Tests to Judge Effects

Insulin	When Injected	Period Covered	Tests Best Reflecting Effect
Short-acting	Before breakfast	Morning	After breakfast and before lunch
Rapid-acting	Before breakfast	Morning	After breakfast and before lunch
Intermediate-acting	Before breakfast	Afternoon	After lunch and before supper
Basal	Before breakfast	Overnight	Before breakfast
Short-acting	Before lunch	Afternoon	After lunch and before supper
Rapid-acting	Before lunch	Afternoon	After lunch and before supper
Short-acting	Before supper	Evening	After supper and before bedtime (snack)
Rapid-acting	Before supper	Evening	After supper and before bedtime (snack)
Intermediate-acting	Before supper or at bedtime	Overnight	Before breakfast
Basal	Bedtime	Overnight	Before breakfast

Basal	Half before breakfast and half before bedtime	Overnight	Before breakfast
Pre-mixed*	Before breakfast	Morning and afternoon	After breakfast and before lunch and after lunch and before supper
Pre-mixed*	Before supper	Evening and overnight	After supper and before bedtime (snack) and before breakfast
Ryzodeg 70/30	Before breakfast	Morning and overnight	After breakfast and before lunch and before breakfast the next day
Ryzodeg 70/30	Before supper	Evening and overnight	After supper and before bedtime (snack) and before breakfast the next day

*With exception of Ryzodeg 70/30

6. Bedtime snacks

To mitigate the chances of overnight hypoglycemia, a small bedtime snack (100-150 calories containing some protein) is strongly recommended. Hypoglycemia, whenever it occurs, often makes patients reluctant to increase insulin doses even though the pattern of SMBG readings clearly indicate that increases are necessary. It is particularly alarming, and potentially more dangerous, when it occurs overnight. The longer the period of not eating, the more risk for hypoglycemia. For example, a patient who eats supper at 6 PM and breakfast at 8 AM has 14 hours without food. If a small bedtime snack is ingested at 11 PM, that period is reduced to 9 hours and the risk for hypoglycemia is much reduced.

The argument against a bedtime snack is that most type 2 diabetic patients (and increasing numbers of type 1 diabetic patients) are already overweight/obese so why provide them extra calories. First, they are counseled to move those calories from supper to bedtime, thereby not increasing their caloric intake. Second, even if they do not completely do so and gain a few extra pounds, that small amount of extra weight will hardly increase their cardiovascular disease risk very much, e.g., a 5 foot 10 inch man increasing from 220 lbs to 225 lbs or even 230 lbs. The benefit of a reduced risk for overnight hypoglycemia seems important enough to offset any deleterious effect of a small weight gain.

If patients accept the recommendation for a small bedtime snack, they must take it consistently. As mentioned above, insulin dose adjustments require a consistent food intake as possible and this is especially true for bedtime snacks. In the example above, an extra 5 hours without food can have an important effect on fasting plasma glucose (FPG) concentrations so that the period without food needs to be relatively consistent.

3. Insulin Preparations

Until recently, all insulin preparations were U-100, i.e., 100 units per ml, with the exception of U-500 regular insulin (500 units per ml). Insulin absorption becomes more variable

as the volume of injectate increases. This very concentrated insulin is used to treat insulin resistant patients who cannot be controlled on more than 200 total units of insulin per day. The smaller injected volume is often more effective and improves control in these patients. With the growing obesity epidemic, which increases insulin resistance and the resultant requirement for larger amounts of insulin, several insulin preparations are now more concentrated (U-200, U-300). There are now more than 20 different preparations of insulin (**Table 2**).

Table 2: Insulin Preparations

PK/PD[1] Description	Generic Name	Brand Names
Short-acting	Regular	Humulin R, Novolin R, Relion R[2]
Rapid-acting	Lispro	Humalog,[3] Ademlog
Rapid-acting	Aspart	Novolog, Fiasp
Rapid-acting	Glusine	Apidra
Rapid-acting	Inhaled insulin	Afrezza
Intermediate-acting	NPH[4]	Humulin N, Novolin N, Relion N[2]
Intermediate-acting	Human R U-500	Same
Basal	Glargine	Lantus, Tuojeo,[5] Basaglar
Basal	Detemir	Levemir
Basal	Degludec	Tresiba[3]
Premixed	70/30	Humulin 70/30,[6] Novolin 70/30,[6] Novolog Mix 70/30,[7] Ryzodeg 70/30[8]
Premixed	75/25	Humalog Mix 75/25[9]
Premixed	50/50	Humalog Mix 50/50[10]

[1]Pharmacokinetic/Pharmacodynamic; [2]Available at Walmart; [3]Also available as U-200; [4]Neutral Protamine Hagedorn; [5]Only available as U-300; [6]70% NPH/30% regular; [7]70% aspart protamine suspension/30% aspart; [8]70% degludec/30% aspart; [9]75% lispro protamine suspension/25% lispro; [10]50% lispro protamine suspension/50% lispro;

Only NPH and regular insulin are human insulins, i.e., their amino acid structures are identical to the insulin produced by the human beta cell. All of the other insulins are analogue insulins, i.e., one or several of their amino acids have been changed (and some are complexed to other molecules) to change their pharmacokinetic/pharmacodynamic (PK/PD) characteristics. Intermediate-acting insulins (with the exception of U-500 regular insulin) are formulated by attaching insulin to the protein protamine. After injection, insulin is slowly released from protamine which accounts for its delayed PK/PD pattern. Regular insulin attached to protamine yields NPH insulin. Rapid-acting analogue insulins attached to protamine confer the same PK/PD characteristics as shown by NPH insulin.

In 2014, the author reviewed 60 randomized control trials (RCTs) comparing analogue vs human insulins in 11,891 type 1 diabetic patients and 8,643 type 2 diabetic patients [27]. Regarding efficacy, there was only a 0.05% difference in HbA1c levels comparing rapid-acting analogues vs regular insulin and only a 0.04% difference with basal analogues vs NPH insulin taken at bedtime. Regarding hypoglycemia, there were no differences in daytime or severe

hypoglycemia. There was a small, but statistically significant, decrease in episodes of overnight hypoglycemia with basal analogues vs bedtime NPH insulin. Similarly, some studies noted less early overnight hypoglycemia with rapid-acting analogues given before supper compared with regular insulin. However, none of these 60 studies recommended a small bedtime snack. A recent Cochrane Database Systemic Review meta-analysis comparing RCTs of rapid-acting analogues with regular insulin in type 2 diabetic patients confirmed no difference in efficacy nor in hypoglycemia [28]. Thus, there are minimal clinical differences between human and analogue insulins.

Insulin costs in the United States have tripled from 2001 to 2012 [29] and doubled further between 2012 and 2016 [30]. This has led to 25% of insulin-requiring diabetic patients rationing their prescribed insulin doses [31]. There have even been a few deaths from diabetic ketoacidosis in type 1 diabetic patients [32]. Analogue insulins cost approximately 2.0-2.5 times as much as human insulins [33]. Furthermore, one can purchase human insulins at Walmart (without a prescription) for $25 per vial. Therefore, if cost is a consideration, using human insulin should prevent patients from skimping on the amount of insulin that they are prescribed.

4. Candidates for Insulin

The following 2, or possibly 3, cohorts of patients should receive insulin.

1. Overt type 1 diabetes: these usually lean patients present with moderate to marked hyperglycemia, often with ketosis, and many are symptomatic. Note that although the usual age of discovery is pre-teen or early teens, some patients can present as adults, even over the age of 60 years. Also note that because of the obesity epidemic, about half of the patients diagnosed with diabetes in adolescence have type 2 diabetes, not type 1. They usually are obese, have a strong family history of diabetes and are often African American or Latino.

2. Type 2 diabetic patients who have failed non-insulin medications : As explained previously, insulin secretion in many of these patients will eventually fall to levels that will not allow a combination of non-insulin drugs (even up to 4 to 5 of them) to provide near euglycemia. Currently, 25-30% of diabetic patients in the United States are taking insulin although many more should be receiving it.

3. Latent Autoimmune Diabetes in the Adult (LADA): These individuals, again mostly lean, present in the 3rd to 5th decades, but without ketosis. They are often initially diagnosed as type 2 diabetic patients. Indeed, about 10% of diagnosed type 2 diabetic patients are positive for antibodies to glutamic acid decarboxylase (GAD), the most common autoantibody in type 1 diabetic patients. Family histories can be very helpful to delineate lean type 2 diabetic and LADA patients. Lean type 2 diabetic patients will most often have a strongly positive family

history in 1st degree relatives whereas LADA patients have type 1 diabetes, and consequently, their family history of diabetes is much more likely to be negative in 1st degree relatives. LADA patients fail non-insulin medications and require insulin more quickly than type 2 diabetic patients. However, because of the major change in lifestyle that is required of patients receiving insulin, the author uses non-insulin drugs as long as they control these patients but quickly transitions them to insulin as soon as they fail.

4. The ADA recommends considering the early introduction of insulin with evidence of catabolism (weight loss) or symptomatic hyperglycemia, or even in the absence of symptoms if either the HbA1c or blood glucose levels exceed 10% or 300 mg/dl, respectively [33]. However, insulin is unnecessary in newly diagnosed type 2 diabetic patients whether they have symptoms or not. In those that are asymptomatic, regardless of HbA1c or blood glucose levels, metformin will usually bring them under control although a minority may need a second non-insulin drug. Even newly diagnosed patients who are markedly symptomatic and have HbA1c levels far above 10% with blood glucose exceeding 400 mg/dl do not require insulin. Nearly 25 years ago, it was shown that maximal doses of a sulfonylurea (SU) (metformin was not available in the United States at that time) would quickly bring markedly symptomatic, hyperglycemic, newly diagnosed patients under control [34]. Most often, the SU dose had to be down titrated after several weeks. Subsequently, 2 randomized control trials found a similar response to large doses of an SU compared with insulin in markedly hyperglycemic, newly diagnosed type 2 diabetic patients [35,36]. Over many years, the author has successfully treated nearly 400 of these newly diagnosed patients (mostly from a medically underserved, minority population) with a maximal dose of an SU. Since metformin cannot be introduced at a maximal dose because of its gastrointestinal side effects, its dose is gradually increased resulting in the frequent need for reducing the SU dose and often discontinuing it (**Figure 1**).

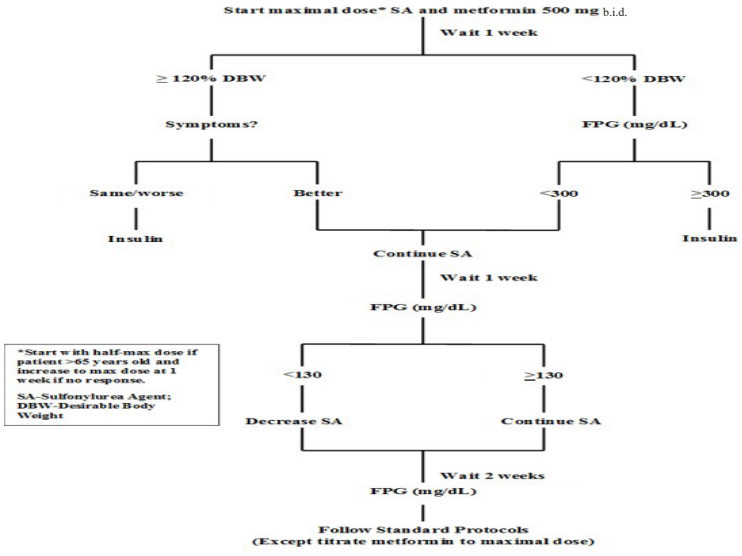


Figure 1: Flow diagram for treatment of markedly symptomatic, newly diagnosed type 2 diabetic patients. Reproduced from chapter 3 in Davidson MB, Hsia S: Meeting the American Diabetes Association Standards of Care: an Algorithmic Approach to Clinical Care of the Diabetes Patient. American Diabetes Association, Alexandria, VA, 2017.

Not only is starting insulin a major lifestyle change for patients, requiring intensive education for insulin administration and SMBG testing, it requires frequent interactions between physicians and patients. Furthermore, after control is achieved, these patients can almost always be controlled on non-insulin drugs which requires more frequent interactions to wean them off of insulin. The approach described in **Figure 1** avoids all of these issues and is uniformly effective in newly diagnosed type 2 diabetic patients.

5. Glucose Targets

Table 3A presents the glucose targets recommended in the guidelines of several diabetes organizations, which vary considerably. Until recently, the pre-prandial target of the ADA was 70-130 mg/dl which was consistent with their still current definition of hypoglycemia as <70 mg/dl [37]. (Many studies have confirmed that the body's response to hypoglycemia does not begin until glucose concentrations are <70 mg/dl.) It was recently changed to 80-130 mg/dl because it was felt that this range was a more accurate reflection of the relationship between mean glucose concentrations and HbA1c levels this leads to the problem that glucose readings between 70 and 80 mg/dl would be considered as low readings in a pattern analysis resulting in a less aggressive approach to adjusting insulin doses.

The author's suggested more stringent glucose targets are presented in **Table 3B**. Although the diabetes organizations do not provide a separate before bedtime (snack) target, some clinicians prefer a slightly higher target to protect against overnight hypoglycemia. Furthermore, the ADA [37] and the American Association of Clinical Endocrinologists [38] have suggested more personalized HbA1c targets. A more stringent target of <6.5% might be considered in selected individuals if it can be achieved without significant hypoglycemia. On the other hand, a less stringent target of >8.0% is suggested for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications or cognitive dysfunction. The suggested glucose targets in **Table 3B** reflect these different HbA1c targets.

Table 3: Glucose Targets (mg/dl)

A - Diabetes Organizations' Recommendations			
	Preprandial	Postprandial	
ADA	80 - 130	<180	
AACE	70 - 130	<140	
IDF	<115	<160	
B – Author's Suggestions			
Control	**Preprandial**	**Postprandial**	**Before Bedtime***
Tighter	70 - 110	110 -140	80-140
Standard	70 – 120	120 - 160	90 – 140
Looser	100-150	150 – 200	120 – 170

6. Hypoglycemia

Hypoglycemia is an obvious very important factor in making decisions regarding adjusting insulin doses. Documented evidence of hypoglycemia via SMBG readings is preferred but realistically many patients will simply treat themselves when they feel the symptoms. As described in **Table 4**, many of these symptoms are non-specific and it can be difficult to ascertain that they were really due to hypoglycemia. (These catecholamine-induced non-specific symptoms are seen in both hypoglycemia and anxiety.) An extremely important question to ask is whether the patient ingested some carbohydrate to treat it, and if so, did the symptoms improve within 15 to 20 minutes? If not, the episode was probably not hypoglycemia and should be discounted in deciding on insulin dose adjustments.

Whether documented or ascertained by history, it is also extremely important to decide if the hypoglycemic episode was explained or unexplained. Explained hypoglycemia occurs if a meal is delayed, missed or less than the usual amount of food is eaten or unanticipated exercise takes place, or occasionally, if a higher than prescribed dose of insulin is taken. Consistency of lifestyle needs to be stressed in this case and the episode not considered in the pattern analysis. Unexplained hypoglycemia occurs in the presence of the patient's usual eating and exercise patterns. In this case, the episode should be accepted as a bona fide hypoglycemic one that is counted in making insulin dose adjustment decisions.

Table 4: Signs and Symptoms of Hypoglycemia

Autonomic*	Neuroglycopenic†
Weakness	Headache
Sweating	Hypothermia
Tachycardia	Visual disturbances
Palpitations	Mental dullness
Tremor	Confusion
Nervousness	Amnesia
Irritability	Seizures
Tingling of mouth and fingers	Coma
Hunger	
Nausea‡	
Vomiting‡	

*Caused by increased activity of the autonomic nervous system;
†Caused by decreased activity of the central nervous system
‡Unusual

7. Insulin Dose Adjustment Principles

Descriptions of insulin therapy almost always include the PK/PD characteristics of the various classes of insulin (**Table 5**). However, given the 20-30% day-to-day intra-individual variability in the response to insulin mentioned previously [25,26], these relatively minor PK/PD differences are clinically unimportant. For example, based on the time course of action of regular insulin, classical teaching has been that it should be injected 20-30 minutes before a meal. The results of a study [39] in which patients were randomized to inject regular insulin either 20 minutes or just before a meal and then crossed over to the other schedule is shown in **Figure 2**. They performed SMBG for 6 weeks on each schedule. The SMBG values were virtually identical with both schedules of regular insulin injections. Note the wide standard deviations attesting to the large variability in patients' responses to insulin in a real world setting.

Table 5: Time Course of Action of Insulins

Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)
Short-Acting	0.5-1.0	2-4	4-6
Rapid-Acting	0.15-0.25	1-2	~3
Intermediate-Acting (NPH)	3-4	6-12	~18
Intermediate-Acting (U-500 Regular)	0.5-1.0	7-9	~12
Basal (Peakless) Glargine, Detemir Degludec	Not Applicable		~24 ~20 ~40
Pre-Mixed	Combination of Individual Components		

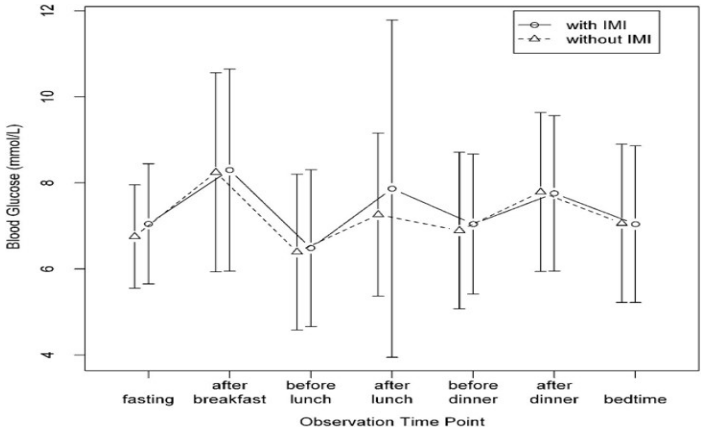


Figure 2: Self monitored blood glucose concentrations (± SD) for 6 weeks following injections of regular insulin just before eating (without an injection-to-meal interval [IMI]) or with a 20 minute IMI. Reproduced from reference 39.

The basic principles of adjusting insulin doses are described in **Table 1**. To reiterate, each component of the insulin regimen has a maximal effect in a different period, i.e., morning, afternoon, evening, overnight. (An exception is a regimen in which NPH insulin is given before breakfast and regular or a rapid-acting insulin is injected before lunch, both of which have their maximal action in the afternoon and therefore is not recommended). The glycemia

of each period is reflected by specific SMBG tests as described in **Table 1**. The dose of each component of the insulin regimen should be changed (or not) depending on the pattern of glucose readings in each period. Since each component has its maximal effect in a different period, changes in one component can and should be made simultaneously and independently of changes in other components of the insulin regimen.

The frequency of daily SMBG testing for insulin dose adjustments is an important issue. The author's suggested frequency for SMBG testing is described in 3b above.

What pattern of glucose values should necessitate a change in an insulin dose? Glucose concentrations during a period are "too high" if the number of values that exceed the upper target level minus the number of values that are less than the lower target level plus the number of bona fide episodes of unexplained hypoglycemia, for which no measured low glucose levels are available, constitute 50% or more of the glucose readings during the dates being considered. As examples, that would be on ≥2/3 days, ≥4/7 days, ≥5/10 days, ≥7/14 days, ≥11/21 days, ≥14/28 days, ≥18/35 days, ≥21/42 days or ≥50% of the values during any number of days under consideration. Once insulin doses become stable, the author prefers to analyze SMBG results at least every six weeks, certainly no more than every 2 months. Some patients become less adherent to the recommended insulin doses and SMBG testing frequency as interactions become less frequent. Furthermore. two-thirds of patients in one year inexplicably required a greater than 20% decrease in their insulin requirements (the average decrease in the insulin dose was 41%) with the period of the decrease lasting 10 weeks [40]. Therefore, infrequent interactions with patients to adjust insulin doses increase their risk for hypoglycemia as well as potentially limiting effective treatment for hyperglycemia.

Conversely, glucose concentrations during a period are "too low" if the number of values that are less than the lower target level plus the number of bona fide episodes of unexplained hypoglycemia, for which no measured low glucose levels are available, minus the number of values that exceed the upper target level constitute 30% or more of the glucose readings during the dates being considered. If the glucose concentrations during a period are neither "too high" nor "too low," no change is made in that component of the insulin prescription that primarily affects SMBG values during that period.

No adjustment is made in that component of the insulin regimen for which the number of appropriate tests is too few. To judge "too few," decide how many SMBG values during a period for the number of days being evaluated would be necessary to change the dose of that component of the insulin regimen that maximally affects that period. The author would suggest that at least one-third of the days being evaluated have SMBG values during the period of time that maximally reflects the component of the insulin regimen that is being considered for a dose adjustment. Fewer values might not accurately reflect the usual eating/exercise pattern of

the patient.

Two factors influence the amount of dose changes, obesity, which causes insulin resistance, and the degree of hyperglycemia. An easy way to define obesity is to use the older definition, which was a body mass index (BMI) of ≥27 kg/m^2. Since Asians have a lower normal BMI range, a value of ≥25 kg/m2 would define obesity in that population. A "very high" pattern of hyperglycemia is defined as the majority of the high values being >70 mg/dl above the high target level and is calculated as follows. First, one has to ascertain that the pattern in a particular period is "too high." Then one examines just the high values and if 50% or more of them are >70 mg/dl above the high target level, that period is designated as "very high." Dose changes are shown in **Table 6** taking into account all of the factors involved. The insulin dose changes to treat periods with very high glucose patterns seem large but unless large increases are used, it will take an inordinately long amount of time to lower these glucose values to within target, especially at the infrequent interactions to adjust insulin doses which unfortunately usually prevails. The author has not had problems with hypoglycemia with these dose increases in patients with very high glucose patterns.

One final caveat. Only one glucose value can be used for each period of each day. Therefore, if both a postprandial and a pre-prandial reading are provided, only one can be used. Similarly, some patients might test more than once in the same period on the same day, e.g., evaluating treatment for hypoglycemia, confirming an unexpected glucose value. The priority for selecting the glucose value to be used in the period for that day (whether pre- or postprandial) in decreasing order should be; a) low, b) very high, c) high and d) within target.

Table 6: Insulin Dose Changes

	Period Pattern*				
	Too Low	Within Target	Too High	Very High	Too Few
Lean	Decrease by 2 units or 10 % whichever is greater	No change	Increase by 2 units or 10 % whichever is greater	Increase by 4 units or 15 % whichever is greater	No change
Obese	Decrease by 4 units or 10 % whichever is greater	No change	Increase by 4 units or 10 % whichever is greater	Increase by 8 units or 15 % whichever is greater	No change

8. Insulin Regimens – Basal Insulin Alone or Bedtime NPH Insulin Alone

There are many classes of non-insulin drugs to treat type 2 diabetes. In the United States, 6 classes are commonly used; metformin, an SU, a thiazolidinedione (TZD), a dipeptidyl peptidase (DPP)–4 inhibitor, a glucagon-like peptide (GLP)–1 agonist and a sodium glucose transporter (SGLT)–2 inhibitor while an alpha-glucosidase inhibitor is also commonly used in Germany and China. Before the advent of the newer classes of non-insulin drugs, i.e., DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, patients were transitioned to insulin when they failed a combination of 2 drugs, metformin and an SU, or sometimes with a 3rd drug, a TZD. Nowadays if the circumstances allow, patients can be given combinations of 4-5 drugs before insulin is added. Recent studies strongly suggest that patients with cardiovascular disease (CVD) should receive certain GLP-1 agonists or SGLT-2 inhibitors [41] and those with heart failure a SGLT-2 inhibitor [41]. Furthermore, several other recent studies have shown that a GLP-1 agonist is just as effective as basal insulin alone in patients failing oral non-insulin drugs [42]. If possible, using a GLP-1 agonist in that situation rather than insulin is simpler for both the patient and the PCP.

Basal insulin alone or bedtime NPH insulin alone is an easy way to introduce insulin therapy to patients who have failed a combination of non-insulin drugs. There is only one insulin injection and initially it is necessary to measure only the FPG level. The goal is to lower these glucose concentrations to target. If there is enough insulin secretion remaining, the non-insulin drugs will control the daytime glycaemia. **Figure 3** illustrates this approach. Type 2 diabetic patients who had failed an SU (metformin was not available in the U.S. at that time) had it discontinued for 4 weeks before bedtime NPH insulin was started and the dose aggressively titrated upward. Enough insulin secretion remained (even though patients were not receiving any non-insulin drugs) that the postprandial rise of glucose was similar at both the markedly elevated and the target FPG concentrations. The HbA1c level decreased from 10.9% to 7.2% in 16 weeks [43].

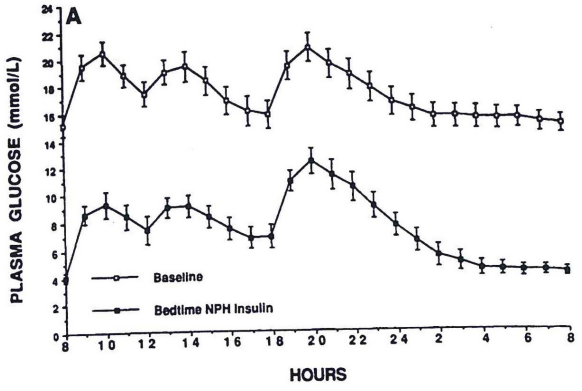


Figure 3: Twenty-four hour plasma glucose levels in type 2 diabetic patients who had failed sulfonylureas at baseline and 16 weeks after adding NPH insulin at bedtime. Reproduced from reference 43.

Obese patients are started on 16 units and lean patients on 10 units of bedtime NPH insulin or one of the basal insulins. Alternatively, the initial dose can be calculated as 0.2 units/kg body weight. These initial insulin doses are almost always less than the patient eventually requires but do avoid overnight hypoglycemia initially which might well discourage the patient from remaining on this therapy. The dose is increased as described in **Table 6**. Ideally, test values should be acted on frequently (every 3-7 days) when insulin is started but as values approach target levels, longer intervals between adjustments are in order. The author prefers adjusting the dose at least once a week for several weeks after starting insulin, every 2 weeks as one titrates the dose upward, every 3 weeks as the dose becomes stabilized and every 6 weeks on an ongoing basis for reasons described previously. Of course, one's practice situation will largely determine the frequency of adjustments.

Many type 2 diabetic patients are very obese and consequently require large doses of insulin to reach target FPG concentrations. Since this can take many months to achieve, the author attempts to teach these patients to self-titrate the insulin dose based on their FPG levels. Obese and lean patients are instructed to increase their bedtime dose by 2 units or 1 unit, respectively, each evening if that morning's glucose value exceeded 130 mg/dl. Conversely, if the value were <70 mg/dl, the dose should be decreased by that amount. Patients on high doses (>80 units) of the U-100 basal insulins (not bedtime NPH insulin) should inject one-half of the dose twice a day since large volumes of injectate can impair absorption [44]. In that case, obese and lean patients are instructed to increase each dose of the basal insulin by 2 units or 1 unit, respectively. Self-titration ceases when there have been no dose changes for one week. Self-titration instructions for patients in English and Spanish are in **Appendix - 1**. The provider can simply circle the appropriate information that applies to specific patients and give it to them.

APPENDIX - 1

Insulin Self-Titration Instructions for Patients

English

A. Instructions for Obese Patients - *English*

<u>Insulins:</u>

- NPH (Humulin N, Novolin N) taken before supper or bedtime
- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before bedtime

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase the insulin dose by 2 units that evening. (If you are taking NPH insulin before breakfast, do not change that dose.)

o Every morning the result is less than 70 mg/dL, decrease the insulin dose by 2 units that evening. (If you are taking NPH insulin before breakfast, do not change that dose.)

o If there have been no changes in the insulin dose for 1 week, do not change the dose anymore.

Insulins:

- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before breakfast

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase the insulin dose that morning by 2 units.

o Every morning the result is less than 70 mg/dL, decrease the insulin dose that morning by 2 units.

o If there have been no changes in the insulin dose for 1 week, do not change the dose anymore.

Insulins:

- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before breakfast AND before bedtime

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase BOTH the morning AND bedtime insulin doses by 2 units each.

o Every morning that the result is less than 70 mg/dL, decrease BOTH the morning AND bedtime insulin doses by 2 units each.

o If there have been no changes in the insulin doses for 1 week, do not change them anymore.

B. Instructions for Lean Patients

Insulins:

- NPH (Humulin N, Novolin N) taken before supper or bedtime

- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before bedtime

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase the insulin dose by 1 unit that evening. (If you are taking NPH insulin before breakfast, do not change that dose.)

o Every morning the result is less than 70 mg/dL, decrease the insulin dose by 1 unit that evening. (If you are taking NPH insulin before breakfast, do not change that dose.)

o If there have been no changes in the insulin dose for 1 week, do not change it anymore.

Insulins:

- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before breakfast

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase the insulin dose that morning by 1 unit.

o Every morning the result is less than 70 mg/dL, decrease the insulin dose that morning by 1 unit.

o If there have been no changes in the insulin dose for 1 week, do not change them anymore.

Insulins:

- Glargine (Lantus, Tuojeo, Basaglar), Detemir (Levemir) or Degludec (Tresiba) taken before breakfast AND before bedtime

o Test blood glucose daily before breakfast.

o Every morning the result is greater than 130 mg/dL, increase BOTH the morning AND bedtime insulin doses by 1 unit each.

o Every morning the result is less than 70mg/dL, decrease BOTH the morning AND bedtime insulin doses by 1 unit each.

o If there have been no changes in the insulin doses for 1 week, do not change them anymore.

Spanish

Tutulación de las dosis de insulina para pacientes

C. Instrucciones para Pacientes con Obesos

Insulinas:

- NPH (Humulin N, Novolin N) que se pone antes de la cena o antes de irse a dormir
- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes de irse a dormir

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar la dosis de insulina por 2 unidades en esa tarde. (Si usted está usando insulina NPH antes del desayuno, no cambie la dosis.)

o Cada mañana que el resultado de la glucosa es menos de 70 mg/dL, disminuir la dosis de insulina por 2 unidades en esa tarde. (Si usted está usando insulina NPH antes del desayuno, no cambie la dosis.)

o Si no ha habido cambios en la dosis de insulina durante 1 semana, no cambie la dosis más.

Insulinas:

- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes del desayuno

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar la dosis de insulina en esa mañana por 2 unidades.

o Cada mañana que el resultado de la glucosa es menos de 70 mg/dL, disminuir la dosis de insulina en esa mañana por 2 unidades.

o Si no ha habido cambios en la dosis de insulina durante 1 semana, no cambie la dosis más.

Insulinas:

- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes del desayuno Y antes de irse a dormir

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar TANTO por esa mañana Y antes de dormir las dosis de insulina por 2 unidades cada una.

o Cada mañana que el resultado de la glucosa es menos de 70 mg/dL, disminuir TANTO por esa mañana Y antes de dormir las dosis de insulina por 2 unidades cada una.

o Si no ha habido cambios en las dosis de insulina durante 1 semana, no cambie las dosis más.

D. Instrucciones para Pacientes Delgados

Insulinas:

- NPH (Humulin N, Novolin N) que se pone antes de la cena o antes de irse a dormir

- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes de irse a dormir

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar la dosis de insulina por 1 unidad en esa tarde. (Si usted está usando insulina NPH antes del desayuno, no cambie esa dosis.)

o Cada mañana que el resultado de glucosa es menos de 70 mg/dL, disminuir la dosis de insulina por 1 unidad en esa tarde. (Si usted está usando insulina NPH antes del desayuno, no cambie esa dosis.)

o Si no ha habido cambios en la dosis de insulina durante 1 semana, no cambie la dosis más.

Insulinas:

- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes del desayuno

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar la dosis de insulina en esa mañana por 1 unidad.

o Cada mañana que el resultado es menos de 70 mg/dL, disminuir la dosis de insulina en esa mañana por 1 unidad.

o Si no ha habido cambios en la dosis de insulina durante 1 semana, no cambie la dosis más.

Insulinas:

- Glargina (Lantus, Tuojeo, Basaglar), Detemir (Levemir) o Degludec (Tresiba) que se pone antes del desayuno Y antes de irse a dormir

o Hacerse la prueba de glucosa en la sangre todos los días antes del desayuno.

o Cada mañana que el resultado de la glucosa es mayor de 130 mg/dL, aumentar TANTO por esa mañana Y antes de dormir las dosis de insulina por 1 unidad de cada una.

o Cada mañana que el resultado de la glucosa es menos de 70 mg/dL, disminuir tanto por esa mañana y antes de dormir las dosis de insulina por 1 unidad de cada una.

o Si no ha habido cambios en las dosis de insulina durante 1 semana, no cambie la dosis más.

Which non-insulin drugs should the patient remain on? Because both insulin and TZDs cause weight gain and sodium retention, the author discontinues a TZD if the patient is receiving one. Otherwise, to maximize the chances that non-insulin drugs will control daytime glycaemia, all of the others should be continued if circumstances allow. Note though that there is a very small (~0.1%) chance of diabetic ketoacidosis in type 2 diabetic patients receiving both insulin and an SGLT-2 inhibitor. However, since using insulin has profound changes for patients' lifestyles (daily injections, potential for hypoglycemia, requirement for SMBG, less flexibility in eating patterns if an intensified insulin regimen is necessary), maximizing non-insulin drugs before insulin is introduced is preferable.

One cannot determine whether basal insulin alone or bedtime NPH insulin alone has failed until target FPG levels are achieved. At that point, there are 2 ways to evaluate the effectiveness of this insulin regimen. The most simple is to wait 3 months and measure a HbA1c level. If at target, continue this regimen. At any time after 3 months that FPG levels are (mostly) at target but HbA1c levels are above target, this regimen has failed. To determine the effectiveness more quickly after initially reaching FPG target levels, have the patient perform SMBG before supper. If the values are consistently >180 mg/dl, the non-insulin drugs are not controlling daytime glycaemia and this regimen has failed. If it were successful soon after

achieving FPG targets, subsequent evaluations could use HbA1c levels.

9. Insulin Regimens – Basal/Bolus

Once basal insulin alone or bedtime NPH insulin alone has failed, an intensification of insulin therapy is necessary. However, before embarking on that course, consider adding a GLP-1 agonist if the patient is not already receiving one. As in patients failing non-insulin drugs in whom RCTs have shown that a GLP-1 agonists is just as effective as basal insulin alone, several RCTs have also shown that a GLP-1 agonist is just as effective as a basal/bolus insulin regimen in patients failing basal insulin alone [42]. Therefore, if possible, a GLP-1 agonist should be tried before embarking on an intensified insulin regimen.

There are 3 intensified insulin regimens to choose from after failing basal insulin alone or bedtime NPH insulin alone; basal/bolus. self-mixed/split or premixed. The basal/bolus insulin regimen consists of a basal insulin or bedtime NPH insulin plus a short- or rapid-acting insulin before meals. It provides the most direct transition from basal insulin alone or bedtime NPH insulin alone and in any case should be chosen for patients with irregular eating patterns. Since the current basal insulin or bedtime NPH insulin dose has achieved the FPG target, that dose should be continued. The initial pre-prandial short- or rapid-acting insulin dose is 2-4 units in lean and 6-8 units in obese patients. These doses almost always need to be increased but starting at this level avoids hypoglycemia which will often discourage patients from continuing this intensified regimen.

Because many patients are understandably reluctant to switch from a 1 injection to a full 4 injection basal/bolus insulin regimen, it has been suggested that initially upon switching to a basal/bolus regimen, short- or rapid-acting insulin only need to be taken before the largest meal [45]. Once the subsequent preprandial glucose target (or before bedtime [snack] if the largest meal is at supper) is reached but the HbA1c level remains above target, short- or rapid-acting insulin is introduced before the next largest meal. This is repeated if the second preprandial bolus injection of short- or rapid-acting insulin achieves the subsequent preprandial glucose target but the HbA1c target is still not reached. At that point, short- or rapid-acting insulin is required before all three meals.

There are two potential problems with this approach. Although logically appealing, it can lead to long delays in reaching target HbA1c levels. First, the target level of glucose, either postprandially or before the subsequent meal (or bedtime [snack] in case supper is the meal in question), must be achieved. Then, at least a further three months must elapse before the HbA1c level will accurately reflect overall glycaemia. This period will be doubled if an injection before a 2nd meal is required and tripled if injections before all three meals are deemed necessary. Since only less than half of patients on basal insulins who begin a basal/bolus regimen by adding a single preprandial bolus dose achieve a HbA1c level of <7.0% [45],

there will be long delays in reaching HbA1c goals in the majority of these patients. Indeed, stepwise increases in the number of preprandial injections showed that 8 months were required for the HbA1c levels to match those achieved in 3 months in patients who were initially placed on all three preprandial injections (**Figure 4**) and only 17% remained on one bolus dose [46].

The second potential problem is that the most important determinant of postprandial glucose concentrations (and therefore the preprandial ones before the next meal) is the starting preprandial level. The increases in postprandial glucose concentrations over preprandial values are similar regardless of the starting preprandial glucose levels [43,47,48]. Therefore, postprandial hyperglycemia is initially best treated by lowering preprandial glucose levels. In the situation where a preprandial injection before a single meal has controlled postprandial glucose concentrations following that meal (and likely the preprandial values of the subsequent meal) but HbA1c levels have not reached target, a 2nd pre-prandial injection must be introduced. However, when the 2nd injection lowers the preprandial values before the largest meal that had just been successfully treated, the short- or rapid-acting insulin dose given before that first meal may be too high leading to postprandial hypoglycemia. The same potential problem occurs when a 3rd preprandial injection is introduced. For these two reasons, the author prefers starting preprandial short- or rapid-acting insulin before all three meals when instituting basal/bolus regimens.

10. Insulin Regimens - Self-Mixed/Split

In the self-mixed/split insulin regimen, the separate NPH and short- or rapid-acting insulin preparations are mixed together in the same syringe and injected before breakfast and before supper. In the author's experience, almost all patients can be taught how to mix insulins if enough time is taken to do so. If used appropriately, the self-split/mixed regimen can yield as tight control as a basal/bolus regimen [49,50]. However, patients have less flexibility with their eating (and exercise) patterns with this regimen, especially with the timing of lunch and supper because the maximal action of the before breakfast NPH injection occurs 6-12 hours later (**Table 6**). To transition from basal insulin alone or bedtime NPH insulin alone, 80% of those total doses become the total daily NPH dose in the self-mixed/split regimen with two-thirds given before breakfast and one-third before supper. This is most often less than the patient will eventually require but avoids hypoglycemia which will often discourage patients from continuing this intensified regimen. Again to avoid hypoglycemia, the maximal initial NPH dose is 40 units before breakfast and 20 units before supper (which corresponds to a bedtime NPH or total basal insulin dose of 75 units). Since almost all patients require short- or rapid-acting insulin to achieve the HbA1c target, a small amount of one of these insulins (2-4 units in lean patients and 6-8 units in obese patients) is added to each NPH injection.

Given that the peak effect of NPH insulin taken before supper occurs between 6 and 12

hours later, as one increases this dose to control the FPG concentration, hypoglycemia may occur overnight before the fasting target is reached. Decreasing the before supper NPH insulin dose may well avoid the overnight hypoglycemia but will work against achieving the FPG target. If the patient is already taking a bedtime snack, that option is not available to avoid the overnight hypoglycemia. In that event, moving the NPH insulin to bedtime will almost always take care of the problem because the peak effect of the bedtime intermediate-acting insulin is closer to breakfast time when the patient is about to eat. This converts the two injection self-mixed/split regimen to a three injection regimen. However, it is often the only way to both avoid overnight hypoglycemia and meet the FPG target without converting to a basal/bolus four injection regimen.

11. Insulin Regimens – Components of Short-/Rapid-Acting Insulin Doses

As discussed previously, patients should be instructed to eat as consistently as possible in regards to the timing of meals and their content of CHO, protein and fat in each meal. Under these circumstances, the preprandial short- or rapid-acting insulin dose (in both the basal/bolus and self-mixed/split regimens) can be broken down into three components. The basic dose is the amount prescribed to be taken before the meal and is the dose that is adjusted based on the pattern of SMBG values described previously. The correction or supplemental dose depends on the preprandial glucose concentration. **Table 7** shows the extra doses added to (or subtracted from) the basic dose to "correct" the preprandial glucose concentrations. Readers familiar with correction doses will note that this schedule suggests progressively increasing extra amounts of short- or rapid-acting insulin for each 50 mg/dl from >150 mg/dl to >350 mg/dl.

Table 7: Initial Correction (Supplemental) Doses of Short- or Rapid-Acting Insulin

Blood Glucose (mg/dl)	Lean	Obese
<70	–1 unit	–2 units
70–150	0 units	0 units
151–200	+1 unit	+2 units
201–250	+2 units	+4 units
251–300	+3 units	+6 units
301–350	+4 units	+8 units
>350	+5 units	+10 units

Evaluating the effect of correction doses is not as straightforward as evaluating the effects of basic doses. To evaluate the responses to the corrections doses, a target range for the subsequent preprandial SMBG value of 100 - 150 mg/dl is used. If the majority of responses to a specific correction dose is >150 mg/dl, the correction dose needs to be increased; if the majority is <100 mg/dl (plus episodes of undocumented unexplained hypoglycemia), it should be decreased. A minimum of three responses to a specific correction dose is necessary before it can be evaluated. For example, if there are five instances where the patient added 2 units

of regular insulin for pre-prandial SMBG values between 201-250 mg/dl, and the subsequent preprandial results were >150 mg/dl on four occasions, the correction dose for this pre-prandial range would be increased to +3 units. In that case, this amount of short- or rapid-acting insulin would be added for the preprandial range of 201 – 300 mg/dl. If subsequent experience showed that this correction dose of +3 units was inadequate for the preprandial range of 251 - 300 mg/dl, the correction dose would be increased to +4 units for this latter range of preprandial values and remain at +3 units for 201 – 250 mg/dl. To simplify the evaluation of correction doses, it is very helpful if patients record the usual dose and the correction dose separately, e.g., 3 + 2, before the meal in a logbook. Regardless of whether a correction dose had been used, all preprandial values with the target levels for the basic doses should be used to evaluate the effect of the basic doses. If preprandial values were consistently high after correction doses, increasing basic doses would still be helpful.

Some patients may also be able to incorporate an anticipatory dose that depends on anticipated meal-related issues or in the several hours following it. For instance, if patients are eating at a Chinese restaurant, they may add a few units (in addition to any correction dose) anticipating a meal with a higher CHO content than usual. Alternatively, if patients are going to engage in more exercise than usual after supper, they may reduce the short- or rapid-acting insulin dose taken before the meal that would have been dictated by the basic and correction doses. There is no formula for anticipatory doses. They must be arrived at empirically based on the patients' ongoing experiences.

In some hospitalized and nursing home patients (and in some cases those residing in a free-living environment), planned meals are incompletely ingested. This increases the chances of postprandial hypoglycemia if the prescribed dose of the short- or rapid-acting insulin is taken preprandially. If this is a recurring situation, a rapid-acting insulin can be taken after the meal is completed without jeopardizing subsequent daily glycemia [51]. With this approach, the patient (or nurse in a supervised environment) will know how much of the planned meal was actually ingested and can estimate how much to reduce the dose of the rapid-acting insulin, i.e., an "anticipatory" change occurring after the amount of the ingested meal is known. The patient (or nurse) should include any correction dose that might have been appropriate in deciding the amount of rapid-acting insulin to inject postprandially, i.e., any meal-related reduction should come from the basic dose.

12. Insulin Regimens – Premixed Insulin

Although premixed insulin preparations obviate the need to have patients mix two different insulin preparations in the same syringe before injection, they have a major drawback. One cannot adjust the doses of the intermediate-acting and short- or rapid-acting insulin separately. For example, because supper is usually the largest meal, a common SMBG pattern in patients

taking a premixed insulin preparation before supper is high before bedtime (snack) glucose concentrations but acceptable values before breakfast the next morning. Raising the before supper dose to lower the before bedtime (snack) levels would jeopardize the before breakfast situation. Note that 70-75% of the increased before supper dose will work mostly overnight and only 25-30% will be available to lower the evening hyperglycemia. Likewise, another common pattern is high before lunch SMBG values but acceptable before supper levels. Raising the before breakfast dose to lower the before lunch tests would facilitate afternoon hypoglycemia. Therefore, achieving near euglycemia with premixed insulins is often not possible, and these insulin preparations should be used only by patients who cannot be taught to mix insulins themselves and for whom no family or other caregiver support is available.

Premixed insulins necessitate different dose changes than described for other insulin regimens in which each component of the regimen can be adjusted independently. With the exception of the rarely used premixed insulin preparation containing 50% of intermediate-acting and 50% of short- or rapid-acting insulin, other premixed insulin preparations contain 70-75% of intermediate-acting and 25-30% of short- or rapid acting insulin. Thus, a dose increase of 4 units would deliver an additional 2.8 units of the intermediate-acting insulin and only 1.2 units of the short- or rapid-acting insulin. Therefore, dose changes of premixed insulins should be 3 and 6 units in lean and obese patients, respectively. If the glucose pattern yields “very high” readings as described previously, the dose increases should be 6 and 10 units, respectively. These dose changes approximate those in a self-mixed/split regimen for the intermediate-acting insulins but are obviously smaller for the short- or rapid-acting insulin components.

To approximate the dose changes in a self-mixed/split regimen in patients treated with 50/50 premixed insulin, dose increases for ”too high” patterns should be 4 and 8 units in lean and obese patients, respectively, and for “very high” patterns, 8 and 16 units in lean and obese patients, respectively.

Since there are two components in premixed insulin preparations, each with a maximal effect during a different period, one must be certain that there is not a “too low” pattern in one of the periods that would be affected by a dose increase in response to a “too high” pattern during another time period. For example, if the evening pattern were “too high” which would require increasing the dose of the before supper premixed preparation, but the overnight period was “too low” as reflected in many low values before breakfast and/or symptomatic hypoglycemic episodes after retiring, not only should the before supper premixed insulin dose not be increased, it should be decreased in response to overnight hypoglycemia. Preventing hypoglycemia in one period takes precedence even when the pattern in another period dictates an increase in the premixed insulin dose.

13. Insulin Regimens – U-500 Regular Insulin

It is not uncommon for very obese type 2 diabetic patients to require hundreds of units of insulin to achieve satisfactory control. Some, in spite of testing appropriately and increasing insulin doses as recommended, are unable to achieve HbA1c levels <8.0% because large volumes of injectate impair insulin absorption [44]. These patients receiving a total of >200 units of U-100 insulins per day can be switched to injections of U-500 regular insulin before breakfast and before supper. The time-course of action of U-500 regular insulin is similar to NPH insulin (**Table 5**). Initial doses and dose adjustments are shown in **Figure 5**. SMBG testing is initially only necessary before breakfast and before supper as the regimen consists of just 2 injections of an intermediate-acting insulin. When FPG values reach target, testing before lunch should be introduced to determine if a separate injection of a short- or rapid-acting insulin before breakfast would be helpful. Similarly, when before supper SMBG glucose values reach target, testing before bedtime (snack) is introduced to determine if a separate injection of a short- or rapid-acting insulin before supper would be helpful. These additional injections convert the U-500 regular insulin regimen from 2 to 4 injections per day. The injections of short- or rapid-acting insulins might be reserved for patients whose HbA1c levels remained ≥7.5% after the before breakfast and before supper SMBG values reach target levels. The author usually starts with 10 units of a short- or rapid-acting insulin and increases their doses as described for obese patients in **Table 6** because inexplicably, many of these patients respond to much lower doses of these U-100 insulins. With this approach, HbA1c levels can usually be lowered to <8.0% and some to <7.5% when switched to the U-500 regular insulin regimen [52,53]. As with NPH insulin, for the occasional patient who suffers from overnight hypoglycemia before achieving target FPG levels as the before supper U-500 regular insulin dose is increased, moving the injection to bedtime can be very helpful. In this situation, however, the patient must ingest a bedtime snack because U-500 regular insulin has a small "postprandial" effect.

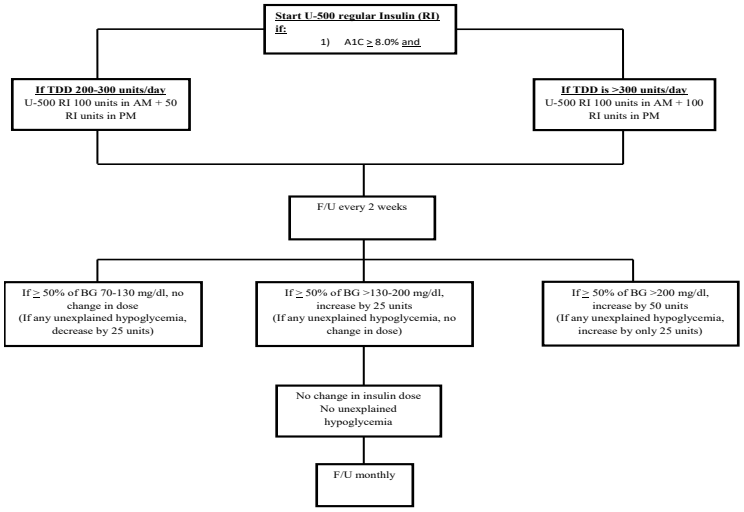


Figure 5: Flow diagram describing the initiation and dose adjustments of Humulin U-500 regular insulin. BG, blood glucose; F/U, follow up; RI, regular insulin; TDD, total daily dose. Reproduced from chapter 3 in Davidson MB, Hsia S: Meeting the American Diabetes Association Standards of Care: an Algorithmic Approach to Clinical Care of the Diabetes Patient. American Diabetes Association, Alexandria, VA, 2017.

14. Insulin Regimens - Intermediate-Acting Insulin Only Before Breakfast

A single morning injection of NPH insulin will seldom achieve near euglycemia. This regimen requires that the single morning injection controls both the before supper and the following morning's glucose concentrations. The usual scenario is that as the morning NPH insulin dose is raised, the before supper glucose concentrations reach target before the fasting values. As the NPH insulin dose is increased still further to lower the next day's before breakfast glucose concentrations, late afternoon hypoglycemia often occurs. The morning NPH insulin dose must then be stabilized or decreased before target FPG levels are reached. At this point, evening NPH insulin must be introduced to improve control further (i.e., the patient is now on the 2 NPH injections of a self-mixed/split regimen, which should have been the initial approach). This scenario would also apply to a single morning injection of the other intermediate-acting insulin, U-500 regular insulin.

There are three exceptions to this scenario. A few type 2 diabetic patients who fail non-insulin medications have FPG values at target or very near target. Their elevated HBA1c levels are due to daytime hyperglycemia, most often manifested by high before supper SMBG results. In that situation, before breakfast NPH insulin is indicated, initially 10 units in lean and 16 units in overweight/obese patients. Eventually, as endogenous insulin secretion continues to decrease, evening NPH insulin often becomes necessary.

A second exception occurs in patients taking large doses of prednisone in the morning only. This steroid will cause daytime insulin resistance but its effect wanes overnight. In this case, many of these patients can be controlled on a single dose of NPH insulin before breakfast although often short-or rapid-acting insulin is also necessary before breakfast and sometimes also before supper.

A third very unusual exception to the requirement of two injections of an intermediate-acting insulin are patients who have a delayed response to NPH [54,55] or U-500 regular [56] insulin, i.e., the peak effect of the morning injection occurs overnight so that the next day's fasting glucose concentration is affected more than the afternoon values. This becomes apparent as the evening dose of the intermediate-acting insulin continues to be decreased because the FPG levels are at target (or even low) until this pattern persists even when no intermediate-acting insulin is taken in the evening. Since the morning injection of the intermediate-acting insulin in this situation works mainly overnight, the preprandial supper (and post-prandial lunch) SMBG readings remain high and the morning dose is usually increased perpetuating the potential for overnight hypoglycemia. Under these circumstances, preprandial short- or rapid-acting insulin is necessary to control blood glucoses during the day. Strangely, there doesn't seem to be a delayed response to the short- or rapid-acting insulins. Thus, the regimen becomes a basal/bolus one with the morning intermediate-acting insulin acting as the basal insulin. The

FPG concentration reflects the action of the previous morning's intermediate-acting insulin whose dose is changed according to the pattern of FPG values and the short- and rapid-acting insulins are adjusted as described in **Tables 1** and **6**.

15. Intensified Insulin Regimens as Initial Therapy

Newly diagnosed type 1 diabetic patients who present in diabetic ketoacidosis (DKA) and hospitalized will be discharged on insulin. However, there are some newly diagnosed type 1 diabetic patients who may not have severe enough DKA to be hospitalized and an intensive insulin regimen will be initiated as an outpatient. Another group of type 1 diabetic patients in whom an intensified insulin regimen may be initiated would be those with LADA failing control with non-insulin medications in whom it is felt that the more gradual approach with a basal insulin alone or bedtime NPH insulin alone would not be effective. Most type 2 diabetic patients will transition to insulin therapy via either a basal insulin alone or bedtime NPH insulin alone but there may be markedly hyperglycemic ones with a long duration of diabetes poorly controlled on non-insulin medications in whom it is also felt that the more gradual approach with a basal insulin alone or bedtime NPH insulin alone would not be effective. Initial doses of the intensified insulin regimens of self –mixed/split and basal/bolus regimens for obese (**Table 8A**) and lean (**Table 8B**) diabetic patients are described. For reasons discussed previously, regimens using premixed insulins are not considered appropriate. As with other regimens, these initial doses are most often less than are eventually required in order to limit hypoglycemia which may discourage patients from continuing with insulin therapy.

Table 8: Initial Insulin Doses for Intensified Regimens

A Obese			
Before Breakfast	**Before Lunch**	**Before Supper**	**Before Bedtime**
20 units NPH/ 4-6 units short- or rapid- acting insulin	-	10 units NPH/ 4-6 units short- or rapid-acting insulin	-
6-8 units short- or rapid-acting insulin	6-8 units short- or rapid-acting insulin	6-8 units short- or rapid-acting insulin	16 units NPH or basal insulin

B Lean			
Before Breakfast	**Before Lunch**	**Before Supper**	**Before Bedtime**
10 units NPH/ 2-4 units short- or rapid- acting insulin	-	6 units NPH/ 2-4 units short- or rapid-acting insulin	-
4 units short- or rapid-acting insulin	4 units short- or rapid-acting insulin	4 units short- or rapid-acting insulin	10 U NPH or basal insulin

16. Intensified Insulin Regimens and Non-Insulin Drugs

The only FDA approved drug for concomitant use with insulin in type 1 diabetic patients is pramlintide. Recent studies have evaluated adding SGLT-2 inhibitors to the insulin regimens of these patients. Although there has been some significant lowering of HbA1c levels (and insulin doses), approximately 5% of patients in these RCTs have experienced DKA [57,58]. To date, this adverse effect has kept the FDA from approving this class of drugs for type 1 diabetes. DKA is likely to be even more common in a real world setting outside of the well-supervised patients in an RCT.

Type 2 diabetic patients are usually started on an intensified insulin regimen when they fail basal insulin alone or bedtime NPH insulin alone. Assuming that the doses of these insulins have been increased appropriately and FPG targets have been achieved, the failure of these regimens is due to inadequate insulin secretion in spite of the accompanying non-insulin drugs as reflected in daytime hyperglycemia. Therefore, adding or maintaining those non-insulin drugs whose effects are mainly mediated by increasing insulin secretion would not seem helpful. In any event, slightly higher doses of insulin would accomplish whatever residual effect these drugs might have. The author does maintain metformin in obese patients, but not in lean ones, to mitigate the initial weight gain seen in patients whose control is improved by insulin (but not for its glycemic effect). Even though the TZDs would enhance the effect of the injected insulin (as well as the remaining endogenous insulin secretion) by reducing insulin resistance, the author does not use them with an intensified insulin regimen because both insulin and TZDs cause weight gain and sodium retention (which increases the risk for heart failure). Since the effect of SGLT-2 inhibitors is independent of insulin secretion, they might well enhance the effect of an intensified insulin regimen, especially postprandially. However, DKA occurred in a small proportion (~0.1%) of type 2 diabetic patients treated with this combination in RCTs [59] so some caution is necessary here. Finally, as mentioned previously, certain GLP-1 agonists and SGLT-2 inhibitors benefit CVD and SGLT-2 inhibitors lower hospitalizations for heart failure. These non-insulin drugs should be maintained (or introduced) in these situations, if circumstances permit.

17. Continuous Glucose Monitoring (CGM)

Most CGM systems now allow patients to view their glucose values in real time and many (especially type 1) diabetic patients adjust their insulin doses in response to the results. Insulin dose adjustments based on glucose patterns as described in this chapter require consistent insulin dosing. Therefore, PCPs caring for patients utilizing CGM who self-adjust their insulin doses will not be able to use this method. However, if patients do not self-adjust or use systems that do not provide glucose readings to the patient, e.g., Abbott's Free Style Libre Pro, this described method could be utilized. For meters that record glucose readings every 15

minutes. patients (or providers) would have to identify the 3 values in the 30 minutes before a meal and the 9 readings from 1 to 2 hours after a meal. For meters that record glucose readings every 5 minutes. patients (or providers) would have to identify the 7 values in the 30 minutes before a meal and the 25 readings from 1 to 2 hours after a meal. The average of these pre- and postprandial glucose values could then be used in the same manner as the SMBG results. A large hurdle in adjusting insulin doses is the lack of glucose information because patients are (understandably) reluctant to test. CGM avoids this problem and if utilized as described would allow PCPs to use the method described in this chapter to adjust insulin doses.

18. Mellitus Health, Inc

At a recent ADA conference entitled "Overcoming Therapeutic Inertia", lack of time and education were identified as the first and third most important contributors, respectively, to therapeutic inertia mellitus [60]. To meet these challenges in insulin-requiring patients, Mellitus Health. Inc (www.mellitushealth.com) has computerized the principles for adjusting insulin doses described in this chapter. These computerized insulin dose adjustment algorithms are FDA cleared [61] and CE mark registered [62]. They can be utilized in 2 ways, either in face-to-face visits or by remote glucose monitoring in which no office visits are required to adjust insulin doses. At office visits, the patient's glucose meter is downloaded into a computer or an electronic health record and within 15 seconds a report appears containing; a) a scatterplot of the glucose values, b) the glucose readings organized before and after each meal and before bedtime, c) an analysis of these results, and d) specific recommendations for possible dose adjustments of each component of the insulin regimen that the PCP can modify or accept. The new insulin doses then serve as the basis for the analysis in the subsequent report.

With remote monitoring, glucose meters are attached to iPhones, and each glucose test result is stored on a secure, HIPAA-approved server. At agreed upon intervals, the readings are analyzed and the same report is generated and sent to the PCP. After deciding on the new insulin doses, either the PCP or a staff person contacts the patient to ascertain that the prescribed insulin doses were taken, inquires about any unusual circumstances (as would be done at an office visit) and relates the new doses to the patient. In a pilot project evaluating remote glucose monitoring carried out at a community clinic serving medically underserved, minority patients who had been taking insulin for at least 6 months with HbA1c levels ≥8.0%, their baseline value of 10.0% decreased to 8.1% 3 months later and was 7.6% at 6 months [63]. The reports were sent to a nurse practitioner at the clinic, and after the initial clinic visit with a staff person to show the patient how to use the remote monitoring system, there were no visits for insulin dose adjustments during the 6 months period. One these reports is shown in **Appendix-2**

Appendix-2

Patient: Patient: 12 35f67237e11f4a0cb992ece944f119fb Visit Date: 06/13/2017 10:43

Patient Info

First Name	Patient: 12	Height	5 ft. 3 in.	Gender	Male
Middle Name		Weight	160 lbs.	Date of Birth	9/10/1958
Last Name	35f67237e11f4a0cb992ece944f119	BMI	28.3		
Patient ID		HbA1c	0.0 %		

Insulin Dosage and Injections

	Before Breakfast	Before Lunch	Before Dinner	Before Bedtime
mir (Levemir)	0 units	0 units	0 units	30 units
[illegible]	0 units	0 units	0 units	0 units

Meal Times and Glucose Targets (mg/dL)

	Eat Breakfast		Eat Lunch		Eat Dinner		Bedtime	
Start / End	8:30 AM	10:00 AM	12:00 PM	1:30 PM	5:00 PM	6:00 PM	9:00 PM	10:00 PM
	Low	High	Low	High	Low	High	Low	High
Before	70	130	70	130	70	130	70	130
After	100	160	100	160	100	160		

Recommendation

Before Dinner: Start 4 Units of your preferred Short or Rapid Acting Insulin
Before Bedtime: Continue 30 Units of Detemir (Levemir)

Warnings

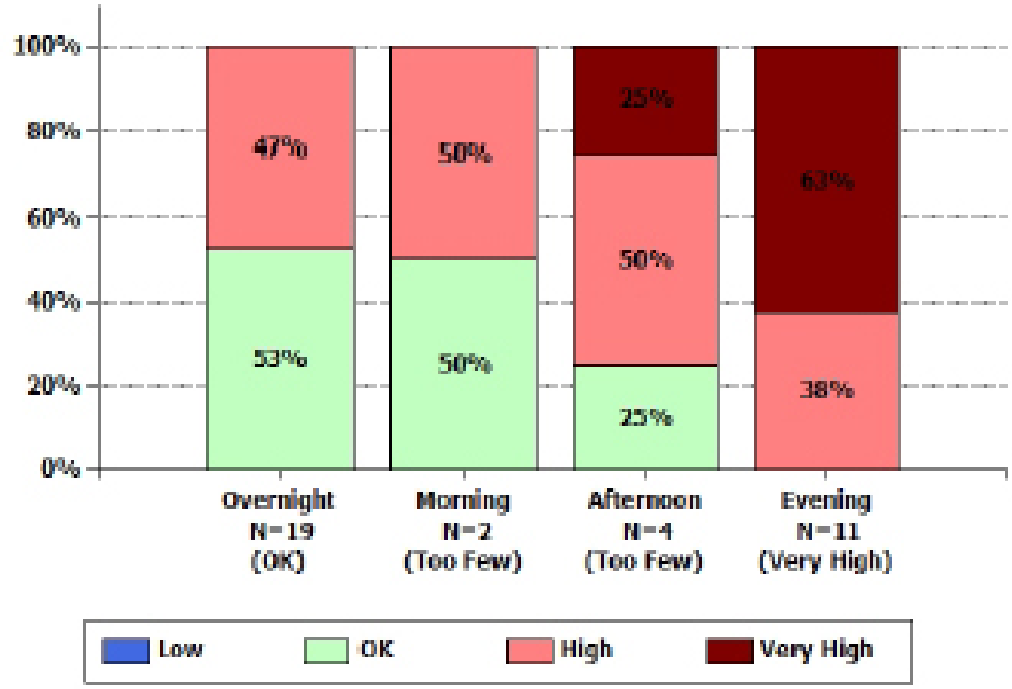
There are too few readings during the morning to analyze and make a recommendation.
There are too few readings during the afternoon to analyze and make a recommendation.

Patient: Patient: 12 33f67237e11f4a0cb992ece944f119fb

Visit Date: 06/13/2017 10:43

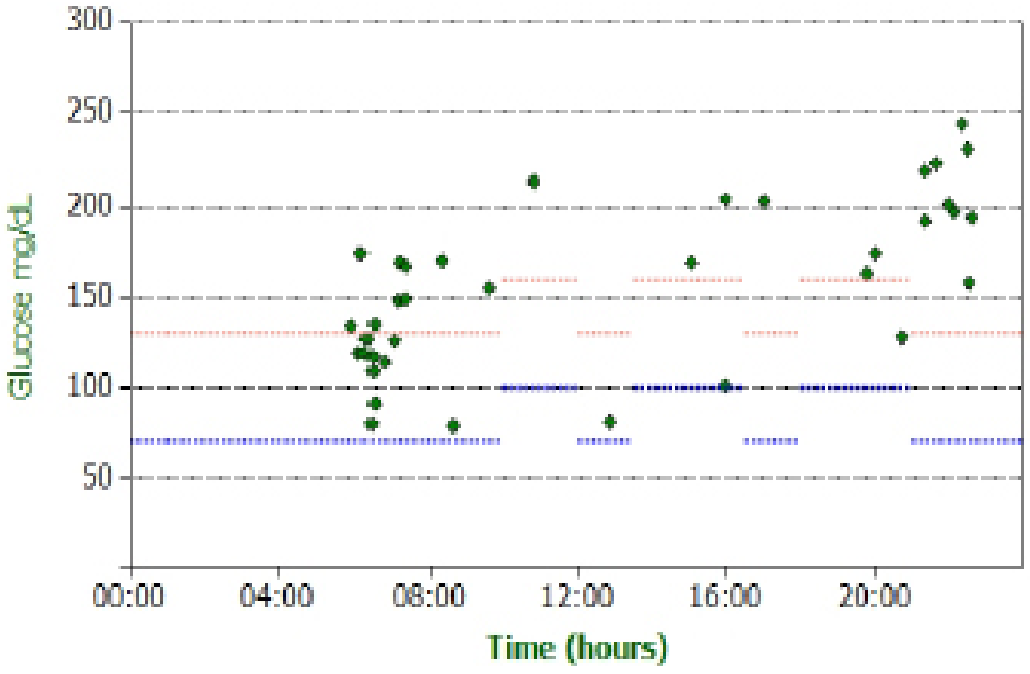
Data Analysis

05/25/2017 to 06/13/2017 (20 days)



Raw Glucometer Readings

05/25/2017 to 06/13/2017 (20 days)



Patient: Patient: 12 35f67237e11f4a0cb992ece944f119fb

Visit Date: 06/13/2017 10:43

Before Breakfast: None -
Before Breakfast: None -
Before Lunch: None -
Before Lunch: None -
Before Dinner: None -
Before Dinner: Start 4 Units of your preferred Short or Rapid Acting Insulin -
Before Bedtime: Continue 30 Units of Detemir (Levemir) -
Before Bedtime: None -

Patient: Patient: 12 35f67237e11f4a0cb992ece944f119fb

Visit Date: 06/13/2017 10:43

Raw readings for period: 05/25/2017 to 06/13/2017 (20 days)

Overnight
5/25/2017 7:09 AM 148 mg/dL
5/26/2017 6:29 AM 109 mg/dL
5/27/2017 6:27 AM 80 mg/dL
5/28/2017 9:35 AM 155 mg/dL
5/29/2017 7:11 AM 169 mg/dL
5/30/2017 6:47 AM 114 mg/dL
5/31/2017 6:20 AM 127 mg/dL
6/1/2017 6:08 AM 119 mg/dL
6/2/2017 7:20 AM 167 mg/dL
6/3/2017 8:20 AM 170 mg/dL
6/4/2017 8:37 AM 79 mg/dL
6/5/2017 7:20 AM 149 mg/dL
6/6/2017 6:32 AM 91 mg/dL
6/7/2017 5:58 AM 134 mg/dL
6/8/2017 6:16 AM 119 mg/dL
6/9/2017 6:31 AM 135 mg/dL
6/10/2017 7:03 AM 126 mg/dL
6/12/2017 6:12 AM 174 mg/dL
6/13/2017 6:29 AM 117 mg/dL

After Breakfast
6/11/2017 10:48 AM 213 mg/dL

Before Lunch
5/30/2017 12:51 PM 81 mg/dL

After Lunch
5/26/2017 3:58 PM 101 mg/dL
5/29/2017 3:58 PM 204 mg/dL
6/1/2017 3:03 PM 169 mg/dL

Before Dinner
5/25/2017 5:00 PM 203 mg/dL

After Dinner
5/30/2017 8:43 PM 128 mg/dL
6/5/2017 7:47 PM 163 mg/dL
6/8/2017 8:00 PM 174 mg/dL

Patient: Patient: 12 33f67237e11f4a0cb992ece944f119fb

Visit Date: 06/13/2017 10:43

Before Bedtime

5/31/2017 9:38 PM 201 mg/dL

6/6/2017 9:21 PM 218 mg/dL

6/9/2017 9:21 PM 192 mg/dL

6/12/2017 9:39 PM 222 mg/dL

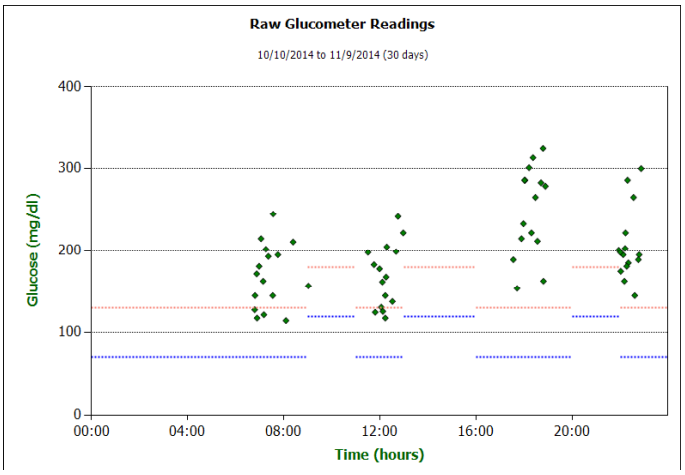
19. Illustrative Cases

Nine illustrative cases of patients on an intensified insulin regimen (3 each for self-mixed/split, basal/bolus and premixed insulins) are presented in **Appendix-3**. The first figure for each case provides the clinical data and a scatterplot of the glucose readings (which is often part of the download of many glucose meters). The pre- and postprandial target levels (blue low, pink high) are shown but for ease of presentation and analysis, all of the values are preprandial ones. The second figure for each case provides the analysis of the glucose values and the recommendations for possible insulin dose changes. Two of the cases have additional comments. The cases illustrate the principles of adjusting insulin doses described in this chapter.

Appendix-3

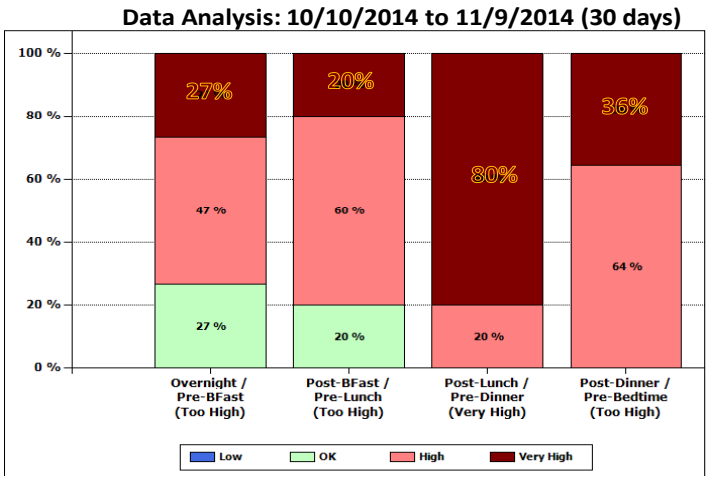
Self-Mixed Insulin Regimen – Case #1

30 NPH/ 10 Reg before breakfast, 20 NPH/10 Reg before dinner; Patient is Obese.



Self-Mixed Insulin Regimen – Case #1

30 NPH/ 10 Reg before breakfast, 20 NPH/10 Reg before dinner; Patient is Obese.

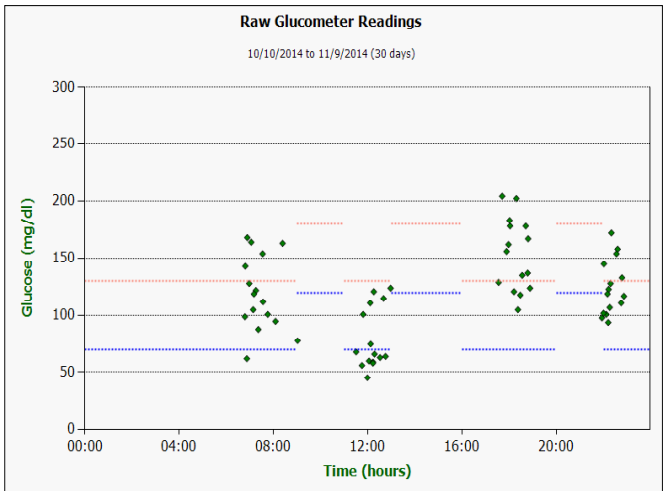


Recommendation

Before Breakfast: Increase Humulin N (NPH) By 8 Units From 30 Units To 38 Units
Before Breakfast: Increase Humulin R (Regular) By 4 Units From 10 Units To 14 Units
Before Dinner: Increase Humulin N (NPH) By 4 Units From 20 Units To 24 Units
Before Dinner: Increase Humulin R (Regular) By 4 Units From 10 Units To 14 Units

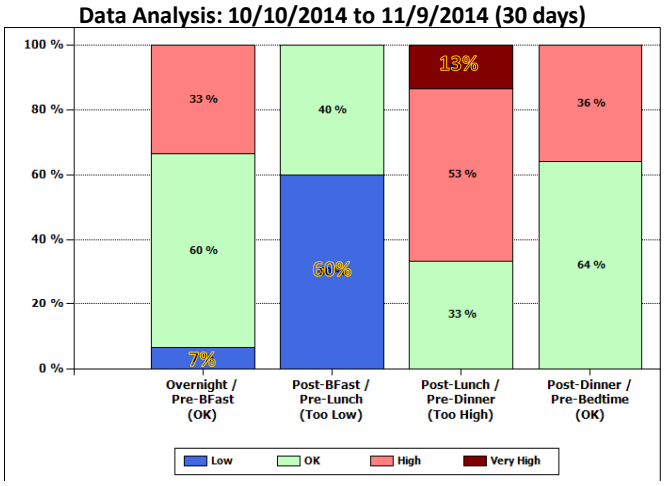
Self-Mixed Insulin Regimen – Case #2

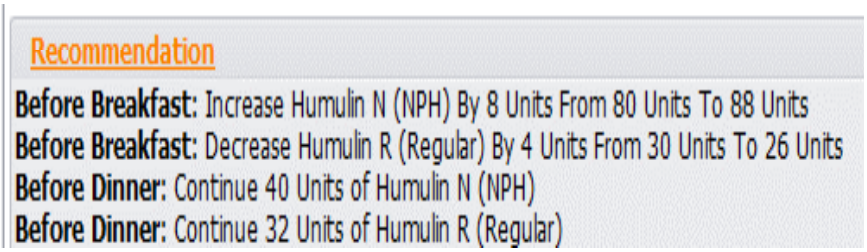
80 NPH / 30 Reg before breakfast, 40 NPH/ 32 Reg before dinner; Patient is Obese.



Self-Mixed Insulin Regimen – Case #2

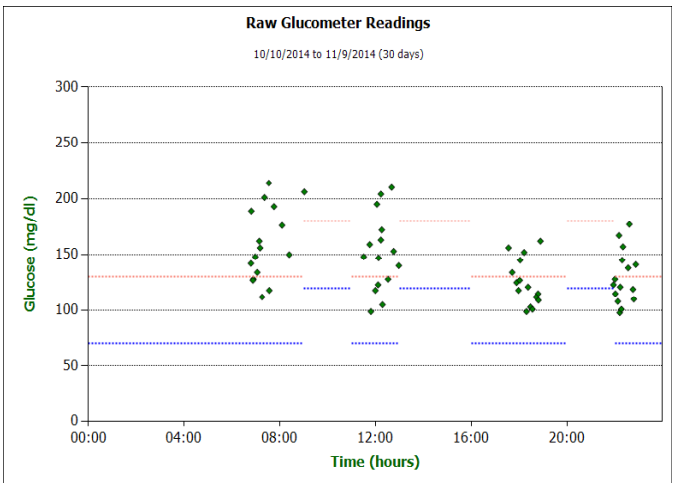
80 NPH / 30 Reg before breakfast, 40 NPH / 32 Reg before dinner; Patient is Obese.





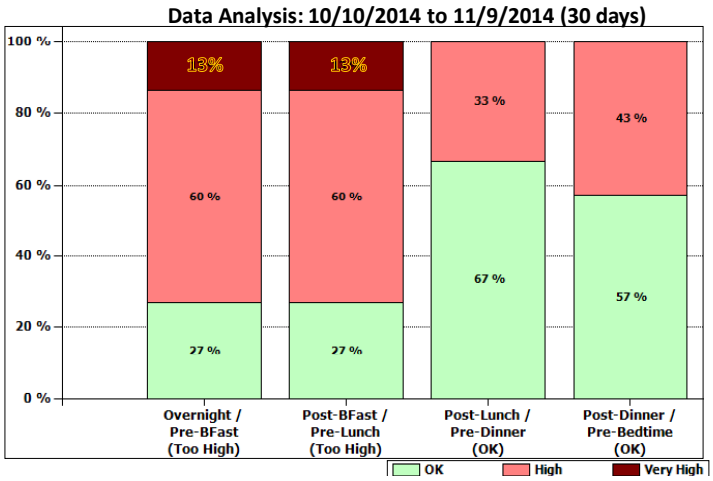
Self-Mixed Insulin Regimen – Case #3

20 NPH / 6 Reg before breakfast, 10 NPH / 8 Reg before dinner; Patient is Lean.



Self-Mixed Insulin Regimen – Case #3

20 NPH / 6 Reg before breakfast, 10 NPH / 8 Reg before dinner; Patient is Lean.

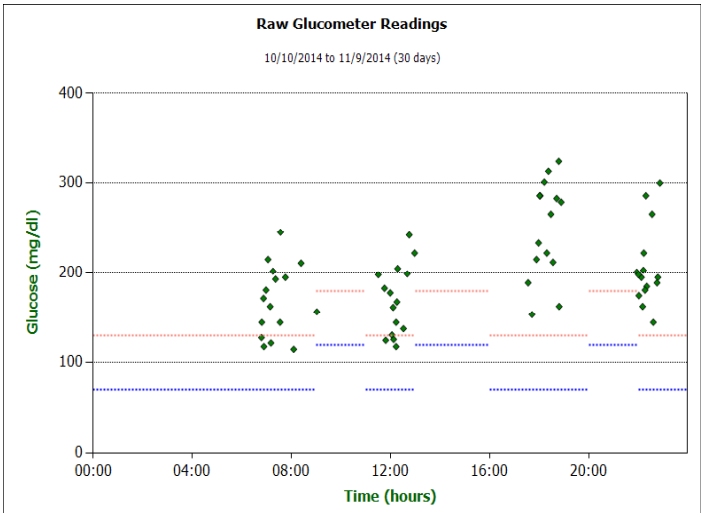


Recommendation

Before Breakfast: Continue 20 Units of Humulin N (NPH)
Before Breakfast: Increase Humulin R (Regular) By 2 Units From 6 Units To 8 Units
Before Dinner: Increase Humulin N (NPH) By 2 Units From 10 Units To 12 Units
Before Dinner: Continue 8 Units of Humulin R (Regular)

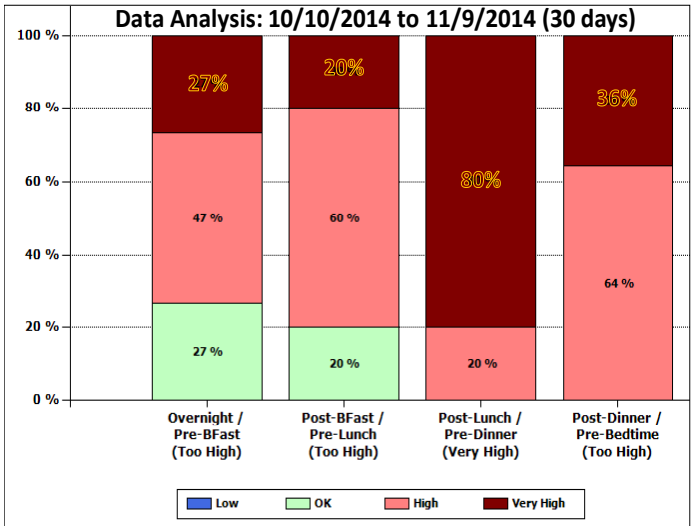
Basal Bolus Insulin Regimen – Case #4 (Patient is Obese)

Lispro-8 before bkft, 10 before lunch, 16 before dinner; 34 Glargine before bed



Basal Bolus Insulin Regimen – Case #4 (Patient is Obese)

Lispro-8 before bkft, 10 before lunch, 16 before dinner; 34 Glargine before bed.

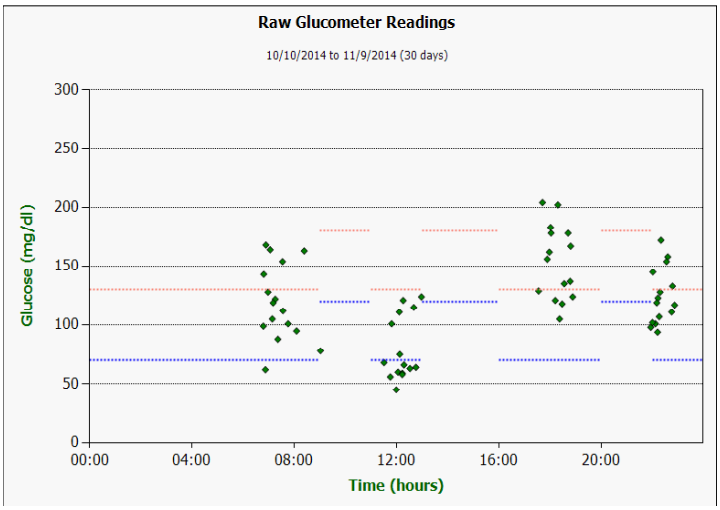


Recommendation

Before Breakfast: Increase Lispro (Humalog) By 4 Units From 8 Units To 12 Units
Before Lunch: Increase Lispro (Humalog) By 8 Units From 10 Units To 18 Units
Before Dinner: Increase Lispro (Humalog) By 4 Units From 16 Units To 20 Units
Before Bedtime: Increase Glargine (Lantus) By 4 Units From 34 Units To 38 Units

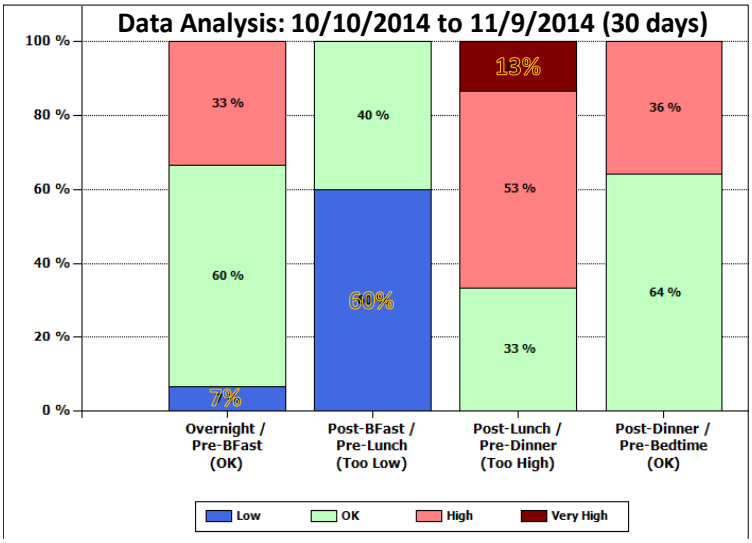
Basal Bolus Insulin Regimen – Case #5 (Patient is Obese)

Lispro-16 before bkft, 20 before lunch, 32 before dinner; 40 Glargine before bkft and bed.



Basal Bolus Insulin Regimen – Case #5 (Patient is Obese)

Lispro-16 before bkft, 20 before lunch, 32 before dinner; 40 Glargine before bkft and bed.

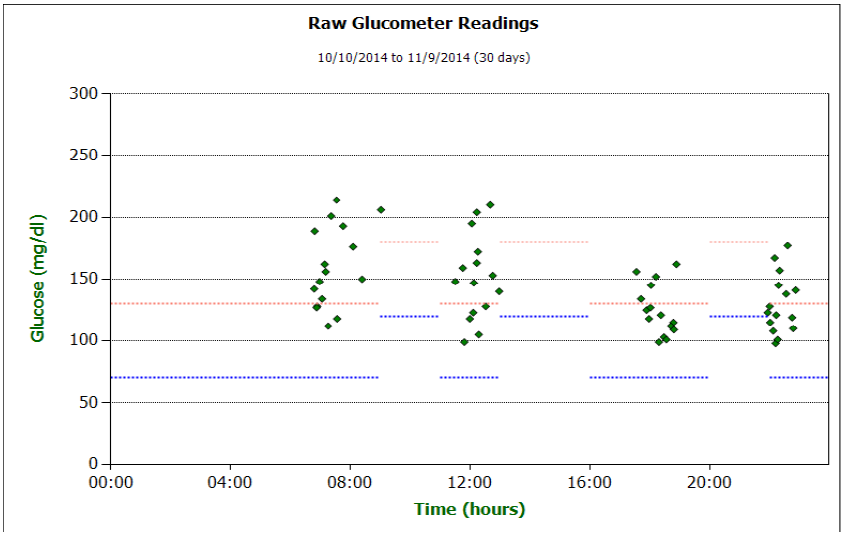


Recommendation

Before Breakfast: Decrease Lispro (Humalog) By 4 Units From 16 Units To 12 Units
Before Breakfast: Continue 40 Units of Glargine (Lantus)
Before Lunch: Increase Lispro (Humalog) By 4 Units From 20 Units To 24 Units
Before Dinner: Continue 32 Units of Lispro (Humalog)
Before Bedtime: Continue 40 Units of Glargine (Lantus)

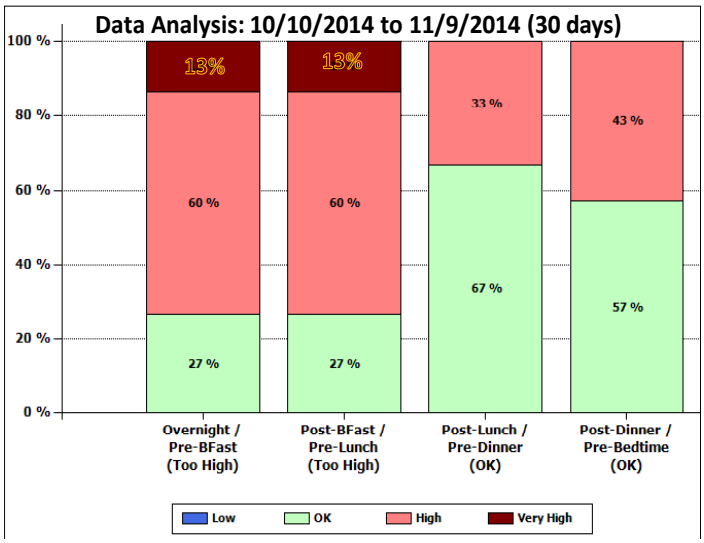
Basal Bolus Insulin Regimen – Case #6 (Patient is Lean)

Lispro-4 before bkft, 6 before lunch, 8 before dinner; 18 Glargine before bed (Hypos 1-3 AM, 2-3 times/week).



Basal Bolus Insulin Regimen – Case #6 (Patient is Lean)

Lispro-4 before bkft, 6 before lunch, 8 before dinner; 18 Glargine before bed (Hypos 1-3 AM, 2-3 times/week).



Recommendation

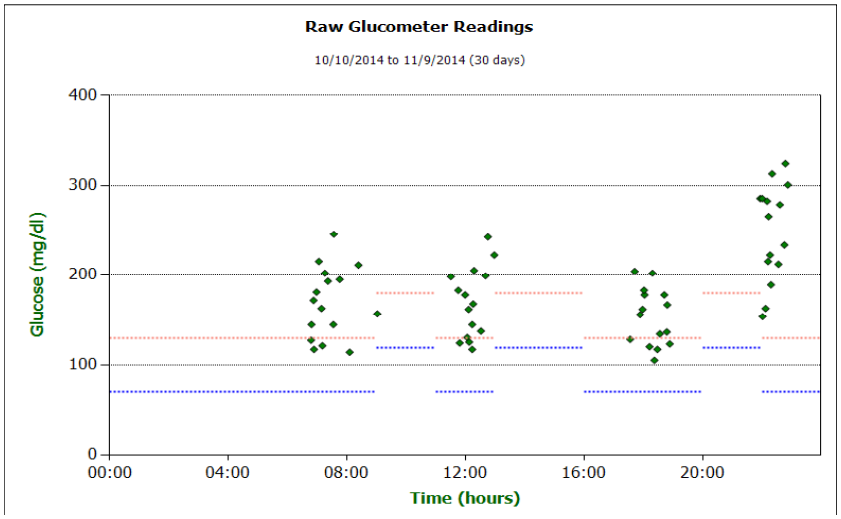
Before Breakfast: Increase Lispro (Humalog) By 2 Units From 6 Units To 8 Units
Before Dinner: Continue 8 Units of Lispro (Humalog)
Before Bedtime: Increase Glargine (Lantus) By 2 Units From 18 Units To 20 Units

COMMENT

The before lunch recommendation has been inadvertently omitted in this case and should have read "Continue 6 Units of lispro (Humalog)" because the afternoon period is OK. Very importantly, note that based simply on the glucose readings before breakfast, the glargine dose should be increased by 2 units as stated. However, the patient gives a history of overnight hypoglycemia which takes precedence over glucose readings and probably accounts for these high readings as secondary to food to treat these episodes and/or the counterregulatory hormone response. **The glargine dose should actually be decreased by 2 units.** This case illustrates the importance of interacting with the patient when adjusting insulin doses.

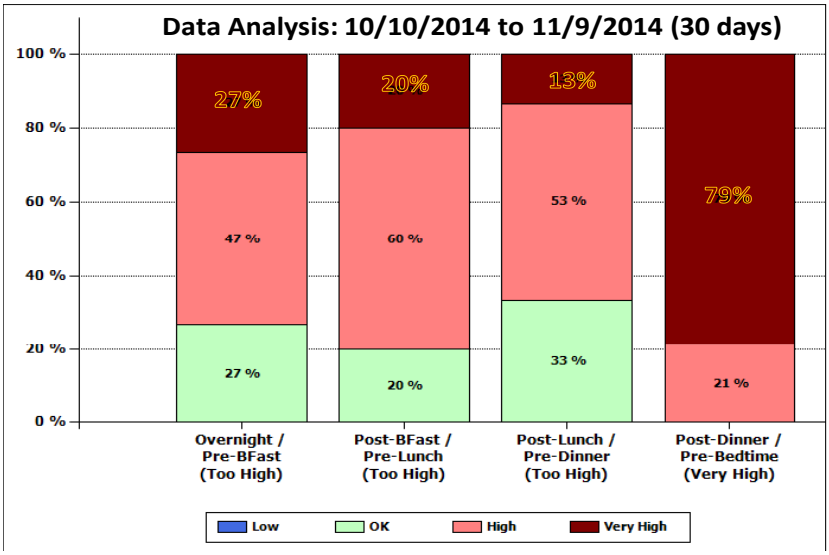
Pre-Mixed (70/30) Insulin Regimen - Case #7

40 Pre-Mixed before breakfast, 30 Pre-Mixed before dinner; Patient is Obese.



Pre-Mixed (70/30) Insulin Regimen - Case #7

40 Pre-Mixed before bkft, 30 Pre-Mixed before dinner; Patient is Obese.

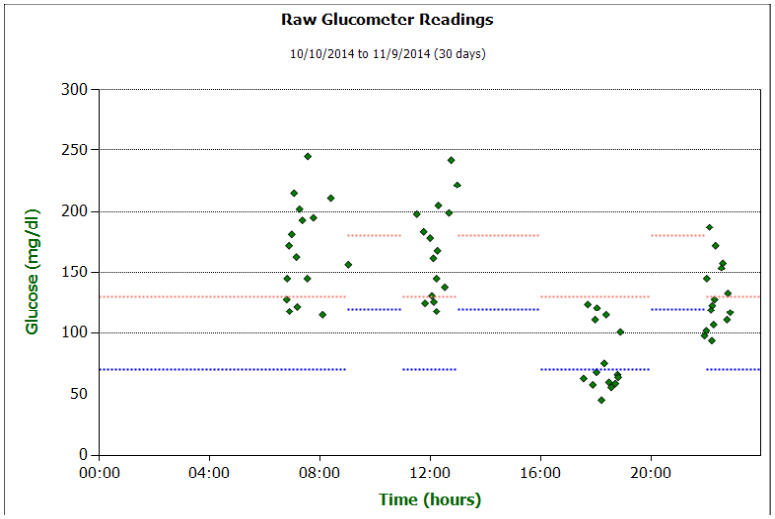


Recommendation

Before Breakfast: Increase Novolin (70/30) By 6 Units From 40 Units To 46 Units
Before Dinner: Increase Novolin (70/30) By 10 Units From 30 Units To 40 Units

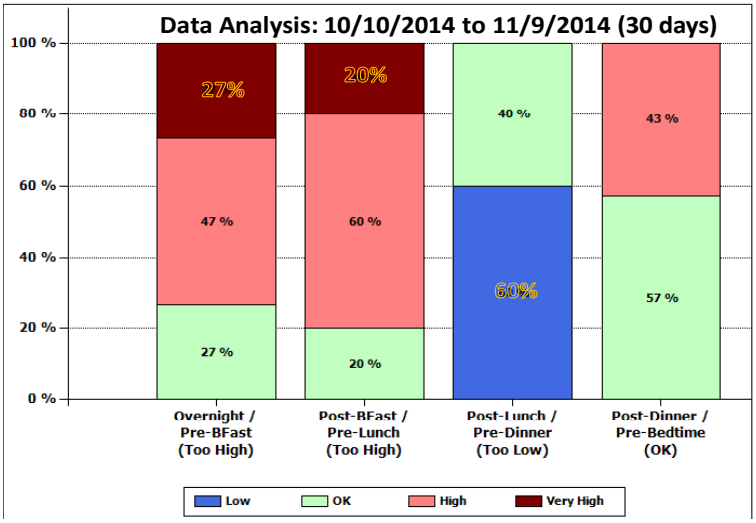
Pre-Mixed (70/30) Insulin Regimen - Case #8

40 Pre-Mixed before breakfast, 30 Pre-Mixed before dinner; Patient is Obese.



Pre-Mixed (70/30) Insulin Regimen - Case #8

40 Pre-Mixed before bkft, 30 Pre-Mixed before dinner; Patient is Obese.



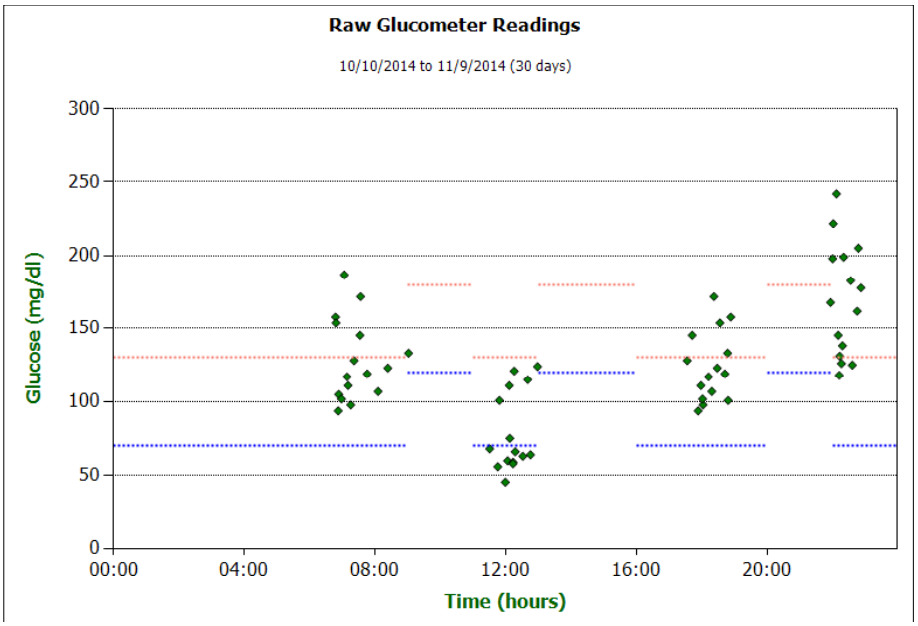
Recommendation

Before Breakfast: Decrease Novolin (70/30) By 6 Units From 40 Units To 34 Units
Before Dinner: Increase Novolin (70/30) By 6 Units From 30 Units To 36 Units

COMMENT
Note that even though the morning period is high and would require more regular insulin before breakfast, the afternoon period being low takes precedence and necessitates lowering the dose of the before breakfast 70/30 pre-mixed insulin.

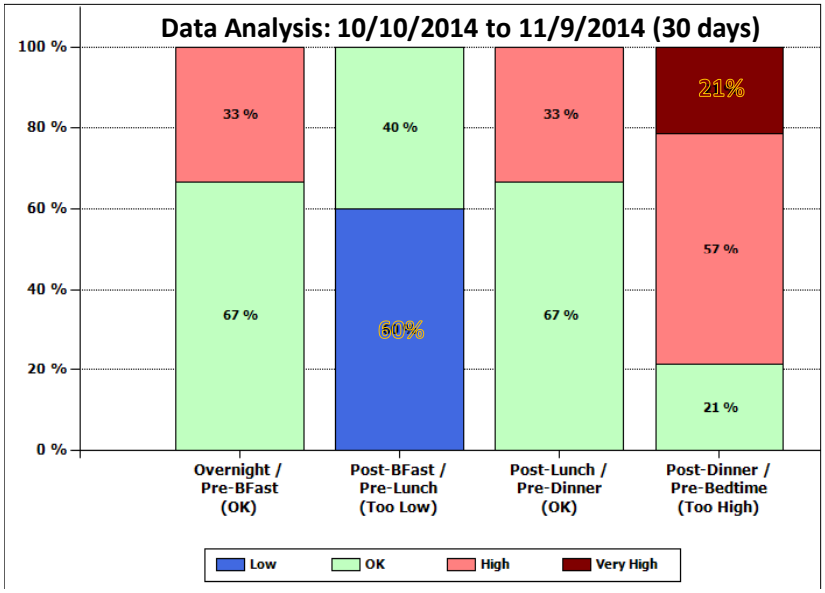
Pre-Mixed (70/30) Insulin Regimen - Case #9

60 Pre-Mixed before breakfast, 20 Pre-Mixed before dinner; Patient is Obese.



Pre-Mixed (70/30) Insulin Regimen - Case #9

60 Pre-Mixed before bkft, 20 Pre-Mixed before dinner; Patient is Obese.



Recommendation

Before Breakfast: Decrease Novolin (70/30) By 6 Units From 60 Units To 54 Units
Before Dinner: Increase Novolin (70/30) By 6 Units From 20 Units To 26 Units

20. References

1. U.K. Prospective Diabetes Study Group. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-1258.

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