CANADIAN CENTRE FOR RESEARCH ON DIABETES
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INSULIN INTENSIFICATION: *Taking Care to the Next Level*

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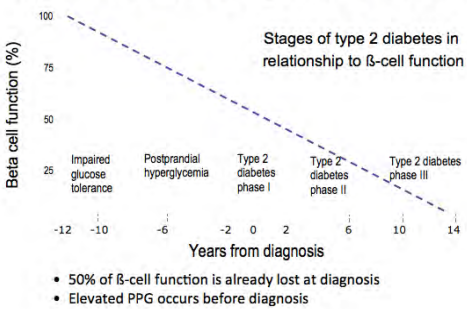
Type 2 Diabetes is an increasing problem in our society, due largely to changes in lifestyle over the past 60 years. The United Kingdom Diabetes Study (UKPDS) in 1998 [1] demonstrated that diabetes is a progressive disease characterized by a combination of insulin resistance and progressive failure of the pancreatic beta cell to produce insulin.

FIG. 1

Type 2 Diabetes is Characterized by Insulin Resistance and Progressive ß-cell Failure



It is estimated that when glucose levels rise to the point that diabetes is diagnosed (FBS >7 mmol/L or PPG >11 mmol/L (3) that 50% of insulin producing ability has been lost and that this loss continues at a rate of about 5% per year on average. [2] When maximal insulin output has decreased to 15 or 20% of normal (6-8 years after diagnosis) glycemic control can no longer be achieved with oral hypoglycemic agents and metabolic instability occurs with increasing glucose levels. At this point insulin supplementation is required in order to achieve control. [3]

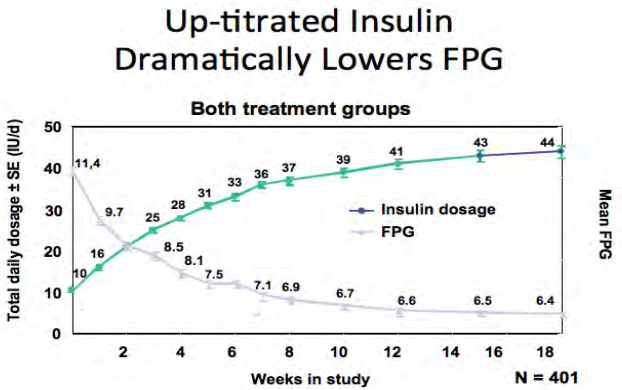
When to start Insulin:

When target A1c <7% can no longer be maintained on oral agents alone.
Hint: After 6-10 years of diabetes, insulin will likely be required.
If A1c is >10%, insulin is needed

BASAL INSULIN:

The first step is initiation of insulin with basal (long acting) insulin together with oral agents. We normally start with 10u of NPH at bedtime or a long acting insulin analogue either insulin detemir (Levemir) or insulin glargine (Lantus). Check fasting glucose daily and then titrate the evening basal insulin dose up by 1u every day until we achieve a fasting glucose level less than 5.5 mmol/L (unless the patient develops hypoglycemia before we achieve a fasting glucose of <5.5; if this happens reduce the dose by 2u until you can re-evaluate). The advantage of long acting analogues detemir (Levemir) or glargine (Lantus) is less hypoglycemia, particularly nocturnal hypoglycemia as well as the convenience of dosing at any time of the day (though the dosing time should be consistent from one day to the next). The advantage of NPH is cost though it should generally be given at bedtime and since the action is shorter, it may have to be dosed twice a day.

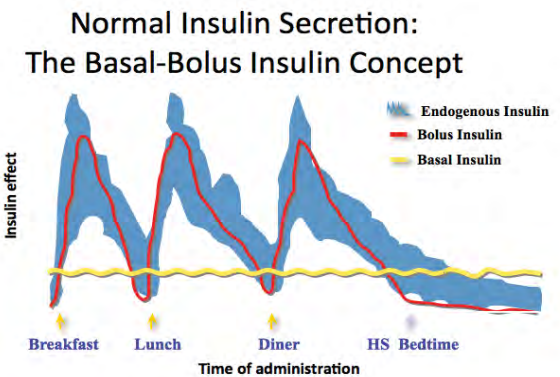
FIG. 2



As insulin deficiency continues to progress, a point is reached where glycemic control (A1c <7%) can no longer be maintained on basal insulin and oral agents. At this point the introduction of short acting insulin to cover insulin needs with meals (bolus or prandial) is required. This article is concerned with the addition of short acting insulin to cover meals when basal insulin alone is insufficient to achieve control.

It may be helpful to think back to the basic physiology of glucose control in the non diabetic individual.

FIG. 3



Basal insulin is secreted at a fairly constant rate throughout the day but in response to the glycemic effect of meals, the pancreas secretes additional insulin to balance this meal effect. In order to decrease post meal glucose elevations (PPG) we need to add short acting insulin to balance the meal effect. A1c is a surrogate measurement of glycemia over a 3 month period. A1c measures average glucose but Monnier (4) has shown that the components of A1c vary according to A1c levels. At near normal levels below 7.5%, 70% of the component of A1c is post prandial glucose; while at A1c levels >9.5%, 70% of the component of A1c is made up of the fasting glucose (FPG). In order to achieve glycemic control we need to consider both fasting and post prandial glucose. We have seen how when we can no longer achieve A1c control <7% on oral agents we add basal insulin and titrate to achieve normal fasting glucose levels. When despite achieving fasting glucose control with basal insulin, A1c remains elevated >7% then it means that we have to address PPG and at this time we need to add mealtime (prandial) mealtime insulin to our basal.

There are several ways of doing this:

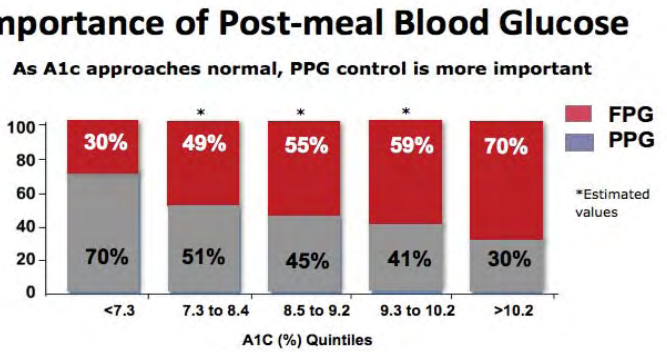
Pre-Mixed insulin: We can replace our long acting basal insulin with a pre-mixed preparation, either NPH & Regular insulin (Humulin 30/70 or Novolin GE 30/70) usually given twice a day at breakfast & supper. These pre-mixed insulins are combinations of 70% intermediate insulin with characteristics of NPH together with 30% short acing (Regular) insulin. The downside to these combinations is that Regular insulin does not peak in activity until about 4 hours after injection so if the injection is given with the meal, there is insufficient insulin effect in the 1-3 hours after the meal when the need for mealtime insulin is greatest resulting in post meal hyperglycemia. The glucose lowering effect of the short acting component then peaks about 4 hours later when insulin needs are less, resulting in hypoglycemia or the need for between meal snacks. The intermediate acting component of the mixture peaks about 6-7 hours after injection so after the evening meal dose, the peak effect of the intermediate component may occur at midnight to 1 AM resulting in nocturnal hypoglycemia. In an effort to overcome these shortcomings of human pre-mixed 30/70 insulin we have developed several analog pre-mixed insulins. The intermediate component is again similar to NPH but the short acting insulin component is an ultra-short acting analogue insulin either insulin aspart (NovoRapid) or insulin lispro (Humalog). These very short acting insulin analogs peak in effect in an hour and have a duration of action of 4 hours; therefore, causing less post meal hypoglycemia. Generally the use of the analogue pre-mixes is preferable to the human pre-mix. There are several analogue pre-mixes available in Canada, those with insulin aspart as the short acting component (NovoMix 30) and those with lispro (Humalog Mix 25 and Humalog Mix 50). The problem with using the pre-mixed insulin is that over time as insulin deficiency becomes more profound, more precise regulation of the short and long acting components is required and ultimately a more precise basal/bolus approach is needed. Nonetheless; the use of pre-mixed insulins, particularly in the elderly or in those unwilling to take the 3 or 4 injections a day of the more intensive regimes may provide adequate control for years and provide a bridge between basal insulin and full intensive management.

As a guideline to dosage, by the time that we make the transition from basal to pre-mix, there has been some loss of glucose control and A1c is greater than 7%. Since more insulin is required overall, we should start at least at the dose that was being given with a basal only regime. Divide the dose in half and give ½ at breakfast & ½ at supper. We then monitor glucose levels before breakfast & supper. If the suppertime glucose is high, increase the breakfast dose (usually in increments of about 10% of total dose), if breakfast time glucose is high, increase the suppertime dose. Usually the person with diabetes can titrate their own insulin dose based on monitoring results but I always suggest that they make an adjustment only after 3 days of consistent glucose readings.

Multiple Daily Injections (MDI) or basal/bolus insulin:

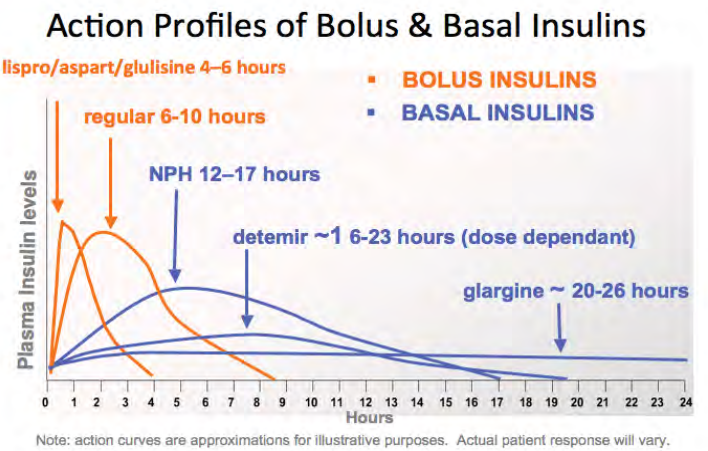
When basal insulin alone is insufficient to achieve glycemic control (A1c <7%), the reason for lack of control is most commonly post prandial hyperglycemia. We know that as A1c gets closer to target, the main component of A1c is post prandial hyperglycemia.

FIG. 4:



The most logical step is to add mealtime short acting insulin. Because of the shortcomings of Regular Human Insulin it is preferable to add a short acting insulin analogue, insulin aspart (Novorapid), insulin glulisine (Apidra) or insulin lispro (Humalog). Physiologically we have a need for both basal (continuous) insulin and mealtime bolus (short acting) insulin. We fulfill the basal need with an extended long acting insulin analogue glargine (Lantus) or detemir (Levemir) usually given once a day or with a twice a day dose of NPH an intermediate acting insulin. There are cost advantages to giving NPH as it is less than half the cost of the long acting analogues but it has a distinct peak activity in 6-7 hours and lasts only 12-16 hours so it is usually given twice a day. The long acting analogues usually give a steady insulin release for 24 hours though with very large or small doses, twice daily dosing may be advantageous. Usually we maintain our basal insulin dose when intensifying to a basal/bolus routine, then add the mealtime insulin as needed. My preferred method of intensification is to continue the oral agents and the basal insulin, then add a small dose of mealtime, short acting analogue insulin at the largest meal of the day (frequently the evening meal). I will start with 5u at suppertime and then titrate this dose up until achieving a normal glucose level (between 4 & 7 mmol/L) at bedtime. Once the suppertime insulin dose has corrected bedtime hyperglycemia and the basal insulin has corrected the fasting hyperglycemia, I will look at the other mealtimes. Often; at first, we can achieve adequate glucose control with basal insulin given once a day and a single injection of bolus insulin with the largest meal of the day. Later as endogenous insulin production further declines we need to give the bolus doses with every meal.

FIG. 5:



Note: action curves are approximations for illustrative purposes. Actual patient response will vary.

If Fasting Glucose is normal and pre-lunch glucose is elevated, add a bolus (mealtime) short acting insulin dose at breakfast. Increase the breakfast insulin dose until a normal glucose level is achieved at lunchtime. As previously it is important not to over react but wait at least 3 days to see consis-

tent glucose values before titrating the bolus (mealtime) insulin. Once a normal glucose level has been achieved at lunchtime, then look at the glucose level before supper, if the pre-supper glucose is high then a bolus insulin dose will also be needed at lunch. Assuming that the pre-lunch glucose level is normal, add a mealtime bolus dose with lunch, titrating this dose up until pre-supper glucose level is normal.

BASAL ADJUSTMENT:

Check glucose levels at bedtime and first thing in the morning before breakfast. If glucose levels increase overnight (consistently) then it usually means that more basal (long acting) insulin is needed. If Glucose levels fall overnight then it usually means that less basal insulin is needed. I ask my patients to check the bedtime & morning glucose readings when we are assessing or adjusting the basal insulin. There is one important caveat and that is the bedtime & morning glucose pair can only be used for adjusting the basal insulin if there has been no bolus insulin or snack within 2 hours of the reading. Very occasionally we see a paradoxical rise in morning glucose levels with increasing bedtime basal insulin. This paradoxical rise may be caused by the Somogyi effect which is the counterregulatory mechanism of the body to undetected hypoglycemia occurring during the night that does not awaken the patient. If we get hypoglycemia during the night we need to reduce the basal insulin dose.

Learning Point: *If glucose rises overnight, increase the basal.*
If glucose falls overnight, decrease the basal.

Once we have established a basal insulin dose and have achieved a normal fasting glucose level, we can look again at adjusting bolus doses. If lunchtime glucose is abnormal, adjust the breakfast insulin. If suppertime glucose is abnormal adjust the lunchtime insulin. If bedtime glucose is abnormal then adjust the suppertime insulin. It is important to adjust insulin only when one can see consistent problems. I usually look for the same pattern at least 3 days in a row before making a change.

Learning Point: *Adjust the bolus insulin by correcting the bolus dose at the previous meal.*

When to stop the oral medication when using insulin:

Metformin can be continued together with insulin. The primary action of Metformin is to reduce glucose load by reducing hepatic glucose formation. It modestly improves insulin resistance and reduces insulin needs, in the UKPDS metformin treatment was also associated with decreased cardiovascular risks. Metformin on its own will not cause hypoglycemia. We usually continue Metformin with insulin as long as there is normal renal function. With moderate renal failure (eGFR <30 ml/min) we reduce the dose to about 50% of maximum therapeutic dose. With severe renal failure (eGFR <15 ml/min) we discontinue Metformin. It is not that Metformin is toxic to the kidney but rather that in the presence of renal failure, individuals are more prone to lactic acidosis and this danger may be accentuated if on Metformin.

Sulphonylurea: May be maintained when on basal insulin but when bolus (mealtime) insulin is introduced there is no point in continuing the sulphonylurea. The effect of the SU is to increase the insulin output of the functioning beta cell but by the time that bolus insulin is needed there is usually very little beta cell function and so it is simpler to discontinue the SU and adjust the bolus insulin dose as needed. Examples of SU are glyburide (Diabeta or Euglucon), gliclazide (Diamicron), glimiperide (Amaryl).

Incretin Therapies [5]

DPP-4 inhibitors: sitagliptin (Januvia), saxagliptin (Onglyza) or linagliptin (Trajenta) act by increasing beta cell insulin output in a glucose dependant manner as well as by reducing Glucagon secretion which in turn reduces glucose formation. By the time that basal/bolus insulin is required there is very little pancreatic insulin secretion so the increased insulin production generated by the increased GLP-1 levels is minimal although Glucagon suppression is still operational. There will still be some glucose lowering attributable to the Glucagon suppression but minimal effect from increased insulin production. The DPP-4 inhibitors may; therefore, still have some beneficial effect though this is minimal and in clinical studies the expected A1c reduction is only about 50% of what we would expect if there were a functioning beta cell so continuing a DPP-4 (Glinide) with basal bolus insulin is frequently not cost effective.

GLP-1 Agonists: Liraglutide (Victoza) and Exenatide (Byetta) have not only the insulin enhancing effect and glycogen reducing effect of the DPP-4 inhibitors but also increase satiety (thereby decreasing food intake) as well as slowing gastric emptying. With severely reduced pancreatic beta cell function there may be minimal increase in insulin production but the other effects of GLP-1 are still operable so there may be logical reasons for continuing a GLP-1 agonist together with insulin but this is not an approved indication though there are currently research studies that have shown complimentary effects of GLP-1 agonist with insulin.

HIGH GLUCOSE ADJUSTMENTS:

In persons with Type 1 Diabetes, where there is almost no endogenous insulin production, CDA Clinical Practice Guidelines recommend intensive insulin treatment with basal, bolus and high glucose adjustments in order to achieve control. In most people with Type 2 Diabetes, there is sufficient endogenous insulin production to smooth out the rough edges. As time passes and insulin production continues to fall; there comes a point at which high glucose adjustments are required since the body has almost no ability to adjust insulin production to gradually treat hyperglycemia. In these individuals; although basal and bolus insulin doses may be adequate, there is no ability to increase insulin production to cover hyperglycemia caused by over indulgence on carbohydrate rich foods or acute changes in insulin needs caused by sickness or lack of physical activity. In these people additional insulin doses to correct hyperglycemia may be needed. This high glucose correction dose is usually given at mealtime or bedtime and is applied if the pre-meal or bedtime glucose is greater than 7 mmol/L. A high glucose adjustment is constructed according to the individual's insulin sensitivity. A typical high glucose adjustment algorithm would be as follows:

If Pre-Meal Glucose is greater than 7 mmol/L take 1 additional unit of
short acting bolus insulin analogue
>8 mmol/L take 2 additional units
>9 mmol/L take 3 additional units etc

CARBOHYDRATE COUNTING: In Type 1 diabetes where there is almost total failure of endogenous insulin production, it is often helpful to match insulin administration more precisely to carbohydrate intake by using the technique of carbohydrate counting. Insulin is given according to a Carbohydrate:Insulin ratio; usually about 1u insulin per 10-15 grams of carbohydrate though the CHO:Ins ratio varies considerably from one individual to another. In people with Type 2 Diabetes who are in the later stages of the disease and have very little endogenous insulin production, carbohydrate counting may help to adjust the insulin dose according to need at every meal, along with a high glucose adjustment in order to achieve adequate glycemic control.

PATTERN MANAGEMENT:

It is very helpful to have the person with diabetes record their glucose readings on a structured basis in a glucose diary. Most glucose monitor manufacturers provide a diary with their meters but diaries may also be found at pharmacies, Diabetes Education Centres or online (e.g. www.diabetesclinic.ca). We encourage the person with diabetes to use the structure of the diary to insert their glucose results, i.e.: use a new line for each day, put the morning fasting glucose value in the column for FBS and any other glucose readings done in the day in the appropriate columns. When PPG readings are taken and recorded, they should be at least 2 hours after the meal. Initially when titrating basal insulin, I ask the patient to measure the Fasting Glucose daily as this figure is used to adjust the basal insulin dose. Later, when we have achieved fasting glucose control, I ask the patient to do at least one other glucose value per day, either before meals or bedtime. I ask the patient if they are able to add up and average the columns of glucose values so that we can get some idea of the pattern of glucose levels. At the next visit we can review the pattern. First we eliminate hypoglycemia. If hypoglycemia occurs during the night or early in the morning then we decrease the basal insulin.

Next we look for the highest glucose values and work toward reducing these, if the highest glucose value occurs in the early morning, then we increase the basal insulin. If the highest glucose occurs at

bedtime then we increase (or start) the bolus insulin dose at supper. If the highest glucose occurs at lunch then we increase (or start) the bolus dose at breakfast. If it occurs at suppertime we increase (or start) the lunchtime bolus. To further fine tune the bolus doses we may wish to selectively check 2 hour post prandial glucose levels, we can use the high glucose adjustment algorithm to treat post prandial hyperglycemia but if there is a pattern of post prandial hyperglycemia after a certain meal we can use this knowledge to adjust the mealtime dose so that post prandial corrections will not be needed as often. It must be remembered that our aim is to achieve A1c levels below 7%, if we have controlled the fasting glucose and yet A1c is still high then more aggressive post prandial control is needed.

CASE STUDIES on pattern Management

1.Premix instead of basal

Betty is a 59 year old who has had diabetes for 8 years, she had been on Metformin 2000 m/day and Glyburide 20 mg a day until a year ago when A1c was 7.8%, FBS 9.5 mmol/L despite oral medications. She was started on Lantus insulin, 10u a day and the dose titrated up until at a dose of 32u a day, FBS came down to 5.3 mmol/L and 3 months later, A1c was 6.8%. Fasting glucose at 6.5 mmol/L is good but A1c has increased to 8.1%.

We discontinued the Lantus and started her on Novomix-30, 17u at breakfast & supper, we titrated the morning dose up until suppertime glucose was less than 7 mmol/L, then we titrated the evening dose until the fasting glucose was less than 7, she is now on Novomix-30, 26u AM & 19u PM, A1c is 6.9%.

2. Basal Plus

Betty is a 59 year old who has had diabetes for 9 years, she had been on Metformin 2000 m/day and Glyburide 20 mg a day until a year ago when A1c was 7.8%, FBS 9.5 mmol/L despite oral medications. She was started on Lantus insulin, 10u a day and the dose titrated up until at a dose of 32u a day, FBS came down to 5.3 mmol/L and 3 months later, A1c was 6.8%. Fasting glucose at 6.5 mmol/L is good but A1c has increased to 8.1%.

Her largest meal of the day is supper so we add on 10u Humalog at suppertime and titrate the supper-time bolus dose up until bedtime glucose level is consistently below 7. She is now on Lantus 32u a day and Humalog 15u at supper, A1c is 6.9%.

3. Basal/Bolus

Betty is a 59 year old who has had diabetes for 10 years, she had been on Metformin 2000 m/day and Glyburide 20 mg a day until a year ago when A1c was 7.8%, FBS 9.5 mmol/L despite oral medications. She was started on Lantus insulin, 10u a day and the dose titrated up until at a dose of 32u a day, FBS came down to 5.3 mmol/L and 3 months later, A1c was 6.8%. Fasting glucose at 6.5 mmol/L is good but A1c has increased to 8.1%.

Her largest meal of the day is supper so we add on 5u Humalog at suppertime and titrate the supper-time bolus dose up until bedtime glucose level is consistently below 7. She is now on Lantus 32u a day and Humalog 15u at supper, A1c is 7.9%.

We ask Betty to measure glucose before lunch & supper, we find that fasting glucose is good at 6.5 but average lunchtime glucose is 8.1 and suppertime glucose is 8.4 mmol/L. We add on 5u Humalog at lunch and supper (and stop her Glyburide), then titrate the breakfast & lunchtime insulin dose until we get pre-meal glucose readings consistently below 7 mmol/L. A1c is now 6.7%.

4. Basal/Bolus +High Glucose adjustment

Betty is a 59 year old who has had diabetes for 12 years, she had been on Metformin 2000 m/day and Glyburide 20 mg a day until a year ago when A1c was 7.8%, FBS 9.5 mmol/L despite oral medications. She was started on Lantus insulin, 10u a day and the dose titrated up until at a dose of 32u a day, FBS came down to 5.3 mmol/L and 3 months later, A1c was 6.8%. Fasting glucose at 6.5 mmol/L is good but A1c has increased to 8.1%.

Her largest meal of the day is supper so we add on 5u Humalog at suppertime and titrate the supper-time bolus dose up until bedtime glucose level is consistently below 7. She is now on Lantus 32u a day and Humalog 15u at supper, A1c is 7.9%.

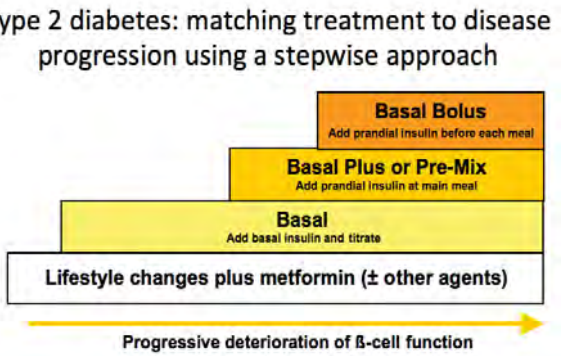
We asked Betty 2 years ago to measure glucose before lunch & supper, we found that fasting glucose was good at 6.5 but average lunchtime glucose was 8.1 and suppertime glucose was 8.4 mmol/L. At this point we stopped her Glyburide and added on 5u Humalog at lunch and supper, then titrate the breakfast & lunchtime insulin dose until we got pre-meal glucose readings consistently below 7 mmol/L. A1c came down to 6.7% but is now back up to 7.4% & we note that her glucose values are labile.

We ask her to check her glucose before every meal and at bedtime, then if pre-meal glucose is :

>7 mmol/L, take 1 additional unit of Humalog with the meal.
>8 + 2
>9 + 3
>10 + 4
>11 + 5
3 Months later, A1c has come down to 6.8%.

TIP: As insulin deficiency increases due to progressive beta cell failure we have to keep increasing the intensity of our treatments.

FIG. 6



SUMMARY: Type 2 Diabetes is characterized by progressive decline in insulin production. After a certain point, glucose control can no longer be achieved on oral agents and metabolic decompensation occurs. At this point as A1c continues to rise despite maximal oral agents, insulin (usually basal insulin) basal insulin needs to be added and titrated up to achieve normal FPG. Over time as beta cell deterioration continues, basal insulin alone is insufficient to maintain A1c less than 7% despite fasting glucose control and mealtime insulin has to be added. With further decline in endogenous insulin production, insulin replacement needs to be intensified to mimic as closely as possible the physiology in normal individuals. Metformin should be retained in people with normal renal function through the progression of insulin therapy but sulphonylureas should be discontinued when bolus (mealtime) short acting insulin is started.

Each of our patients is an individual and each needs individual treatments according to their needs & lifestyle.

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