

Treatment Outcomes with the Use of a Stepwise Insulin Combinations Algorithm Among Type 2 Diabetic Patients

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Abstract

Introduction: In the management of type 2 diabetes, insulin is often started late, when there is failure to achieve good control on maximum oral agents. Clinical inertia to insulin initiation and intensification is widely prevalent in our local setting resulting in poor control of diabetes. This study looked into a stepwise insulin combinations treatment algorithm used in an Endocrinology referral clinic at the University of Santo Tomas Hospital (USTH). It aimed to demonstrate the clinical course of the patients, determine the degree of HbA1c reduction, and show the associated extent of hypoglycemia and weight gain.

Methods: This is a retrospective chart review of 104 patients that used the following stepwise treatment: Oral regimen; Regimen A: basal+oral; Regimen B: basal+premeal bolus TID±oral; Regimen C: premixed aspart 70/30 or lispro 75/25 TID or BID with prelunch bolus, ± oral; Regimen D: premixed 70/30 BID+premeal bolus TID ± oral; Regimen E: premixed 70/30 BID+premeal bolus TID+basal ±oral. All received automatic snacking two hours after main meals to prevent hypoglycemia. Patients were educated on proper diet and

exercise. Data was analyzed using paired t-test, frequencies and percentages.

Results: Most ended on the intensive insulin regimens D 57(55%), and E 18 (17%). Significant HbA1c reduction was demonstrated as follows: Regimen A (n=8): 1.376 ± 0.919 ($p=0.000$), Regimen B (n=18): 2.320 ± 2.177 ($p=0.000$), Regimen D (n=57): 2.197 ± 2.158 ($p=0.000$), Regimen E (n=18): 2.684 ± 1.689 ($p=0.000$). Overall mean weight gain was 1.070 ± 11.435 kg ($p=0.335$). Ten, non-severe hypoglycemia events were reported.

Conclusion: The use of this stepwise insulin combinations treatment algorithm exerted significant HbA1c reduction, with minimal events of hypoglycemia, and statistically insignificant weight gain. Hence, this is a feasible tool that may be used as a guide for intensification of insulin treatment.

Keywords: Diabetes Mellitus Type 2, insulin combinations, HbA1c reduction

Introduction

The goal of treatment of diabetes is to achieve adequate reduction in HbA1c that translates to a decrease in microvascular and macrovascular complications as demonstrated by prospective randomized clinical trials such as the Diabetes Control and Complications Trial (DCCT), and the United Kingdom Prospective Diabetes Study (UKPDS).^{1,2} Lifestyle modification, in the form of diet and exercise, is the initial course of action. This is followed by oral therapy starting with metformin, alone or in combination with other oral agents, or early insulin use.³ The more popular practice is maximizing oral agents, followed by insulin treatment when there is still failure to attain good control.

Several insulin regimens exist. The Treat-to-Target Trial showed that the combination of bedtime basal insulin with oral agents can help achieve HbA1c of 7.0%.⁴ The basal bolus regimen is advocated by Vinagre et al. as a feasible,

effective and safe treatment for patients with long standing diabetes mellitus type 2.⁵ Premixed insulin given as often as three times daily (lispro mix 75/25) was deemed comparable to the basal bolus regimen, and may be an option of diabetes treatment intensification coming from an oral regimen.⁶ There is evidence supporting that therapy with biphasic insulin with rapid acting insulin, by mimicking physiologic insulin secretion, results in sustainable glycemic control.⁷

Conventional and more complex insulin regimens are designed to meet glycemic targets and accommodate the natural disease course of type 2 diabetes mellitus. Since there is progressive loss of β -cell function, and reduced β -cell mass, there is worsening of glycemic control over time,⁸ hence requiring increased dose and alternative strategies of insulin therapy. This study looks into an algorithm used in an Endocrinology referral clinic at the University of Santo Tomas Hospital (USTH) utilizing a stepwise regimen of insulin combinations to decrease HbA1c levels towards desired goals (Figure 1).

Objectives

This study aimed to describe the clinical profile and treatment outcomes of patients who utilized a stepwise insulin combinations algorithm in an Endocrinology referral

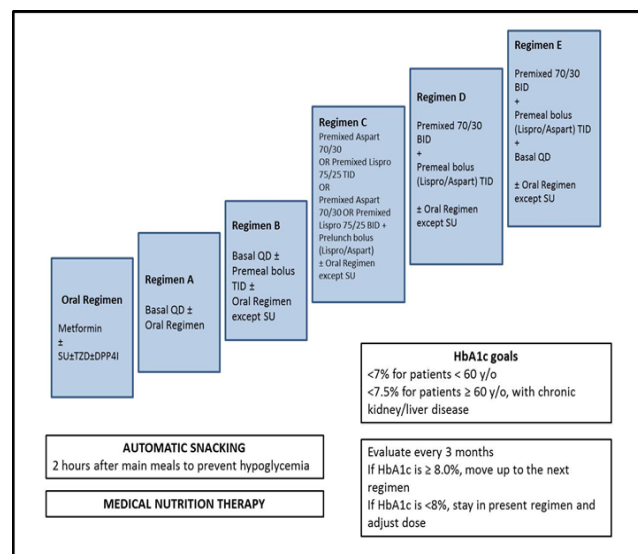
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clinic at the USTH. Specifically, it aimed to demonstrate the clinical course of the patients, determine the extent of HbA1c reduction, to show the associated events of hypoglycemia, and be able to quantify the magnitude of weight gain.

Figure 1. Stepwise Insulin Combinations Treatment Algorithm



*SU-sulfonylurea, TZD- thiazolidinedione, DPP4i- Dipeptidyl peptidase 4 inhibitor

Methods

This is a retrospective study employing a chart review of patients seen in an Endocrinology referral clinic at the USTH, where the Stepwise Insulin Combinations Treatment Algorithm was used, from March 2010 to March 2013, observed within a one-year period. Purposive sampling was employed.

Inclusion criteria were as follows: Patients ≥ 18 years old with diabetes mellitus type 2, with HbA1c ≥ 8.0%. The following patients were excluded from the study: pregnant, patients with conditions affecting HbA1c levels (hemoglobinopathies), anemia with hemoglobin <10 mg/dl, recent blood loss or transfusion, hemolysis, erythropoietin therapy, use of steroids for the past six months, and any acute illness.

The Stepwise Insulin Combinations Treatment Algorithm (Figure 1) consists of a series of regimens starting with purely oral agents, progressing to single, then multiple insulin types. After shifting to a new insulin regimen, the patients were instructed to do self-monitoring of blood glucose (SMBG), usually two hours after main meals in the first one to two weeks to allow for optimal dose adjustment. The patients were monitored by the attending physician either by clinic visit or SMS correspondence, and instructed on the dose adjustment. After the individualized dose is established, an HbA1c check is done in three months, and determined whether a regimen intensification is necessary or not, based

on attainment of set goals.

HbA1c goals were set at <7.0% for those <60 years old, and ≤7.5% for patients ≥ 60 years old, or with chronic kidney disease stages 3 and above, or chronic liver disease.

Hypoglycemia was defined as capillary blood glucose (CBG) ≤70 mg/dl (≤3.9 mmol/L), including probable symptomatic hypoglycemia, an event during which symptoms typical of hypoglycemia are not accompanied by blood glucose determination, but was presumably caused by a plasma blood glucose concentration ≤70 mg/dl (≤3.9 mmol/L). Severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, or take other corrective actions.⁹

The oral regimen simply consists of metformin (MET), sulfonylurea (SU), thiazolidinedione (TZD), DPP4 inhibitor (DPP4i), used singly or in combination, as recommended by the American Diabetes Association and the European Association for the Study of Diabetes. Usually, metformin was the initial choice, with no particular order of subsequent choice(s), but individualized to the unique clinical characteristics of each patient.³

If HbA1c is ≥ 8%, the patient is started on Regimen A, which consists of once daily basal insulin on top of the previous oral regimen. The insulin dose is initiated at 0.2 units/kg body weight (BW)/day, and gradually titrated by adding two units every three days until the pre-breakfast CBG is less than 130 mg/dl. The use of a basal insulin as the first insulin type added to an oral regimen is deemed as reasonable, practical, convenient and effective, supported by the Treat-to-Target trial, and the APOLLO trial.^{3,4,10}

Upon repeat evaluation, if HbA1c is ≥ 8.0%, the treatment is advanced to Regimen B, comprised of once daily basal insulin, pre-meal rapid-acting insulin TID, with or without the previous oral regimen, discontinuing any SU. This is popularly known as the basal-bolus regimen. The total daily dose of insulin (TDD) is calculated at 0.3-1.0 unit/kg BW/day. The lower limit is used for those older than 60 years, or have Chronic Kidney Disease Stage 3 and higher; whereas, the higher limit is used for those who are obese and have long duration of diabetes, and presumably have a higher degree of insulin resistance.¹¹ Fifty percent (50%) of the TDD is given as once daily basal insulin, with the remaining 50% split equally into three pre-meal boluses. The insulin doses are titrated by two units every three days until the two-hour post meal value of <180 mg/dl is attained.¹² This regimen mimics the physiologic insulin secretion in response to hepatic glucose output, and postprandial glycemic excursions. It offers more flexibility and is superior to twice daily premixed insulin regimen in reducing HbA1c as shown by randomized open label trial by Fritsche et al, and a meta analysis by Guigliano et. al.^{13,14}

Regimen C consists of premixed aspart 70/30 or premixed lispro 75/25 given three times daily before meals, or a variation of premixed aspart 70/30 or premixed lispro 75/25 given pre-breakfast and pre-dinner, plus a pre-lunch lispro or aspart bolus, with or without the previous oral regimen. To

calculate for the dose, the TDD is increased by 10-20% from the previous regimen, and divided into the three pre-meal doses, given at roughly the following proportion: 40% pre-breakfast, 20% pre-lunch, and 40% pre-dinner. The dose is incremented by two units until a two-hour post meal capillary blood glucose of <180 mg/dl is attained. This regimen is based on the study of Garber et al. which showed that three daily injections of premixed aspart 70/30 resulted in a 77% achievement of HbA1c of <7.0%¹⁵.

Regimen D consists of premixed human insulin 70/30 twice daily plus a pre-meal bolus of aspart or lispro given pre-meals, with or without the previous oral regimen. Fifty percent of the TDD consists of premixed human insulin 70/30 BID, 2/3 as pre-breakfast and 1/3 as the pre-dinner dose, and the remaining 50% as equally divided pre-meal rapid acting insulin. The dose is increased by two units for each insulin component until a two-hour post meal capillary blood glucose of <180 mg/dl is attained. This regimen was first described by Laplano et al., in a retrospective study, demonstrating a 32% HbA1c reduction from baseline, and sustained good control for more than five years.⁷

Regimen E is basically the same as Regimen D, with addition of a basal insulin given once daily at 0.1-0.2 units/kg BW/day. This is an innovative regimen and has never been described in previous studies, but designed to give an additional basal insulin coverage that is peakless, and lasts for 24 hours. This is adjunctive to a regimen which already has some basal and prandial coverage, but the basal component from the NPH, which wanes after 16 hours or less, although given twice daily, may still be quite insufficient for those who are severely insulin resistant. It is used for the subset of patients who need a TDD of more than 1.5-2 U/kg BW.

For all the regimens, if HbA1c on re-evaluation is <8.0%, the regimen is maintained, but the insulin dose is titrated accordingly. Entry into the stepwise insulin algorithm depends on the antidiabetic regimen the patient is on. For instance, if the patient is already on once daily basal insulin plus oral agents or what is considered as Regimen A in the algorithm, and the HbA1c is $\geq 8.0\%$, the patient will be moved up to Regimen B.

The patients are educated on medical nutrition therapy wherein total caloric requirement per day was based on physical activity (30 kcal/kg/day), and divided into 60% carbohydrate, 15% protein, 25% fats divided into three meals and three snacks. The snacks were taken automatically two hours after each main meal even without hunger. This is the principle of automatic snacking, a strategy that prevents hypoglycemia among patients on intensive insulin therapy.¹⁶ Patients were also encouraged to have a suitable exercise regimen.

The following data were extracted: clinical profile, course of treatment, baseline and final HbA1c during the observation period, events of hypoglycemia and weight gain. Data was analyzed using percentages, frequencies, and paired T-test.

Patients were contacted via telephone call/SMS/email to be informed about the study. Their verbal/expressed consent to use the information in their patient record was obtained via telephone call/SMS or email, and documented. If the patient could not be contacted after reasonable effort has been done to retrieve their contact information, surrogate consent from either the attending physician or the department chair was taken. Included patients' data was entered in a database. The identity of patients were kept confidential by assigning numbers to each patient as identification code. The medical records and database were accessible only to the investigators. This study was carried out in accordance with the Declaration of Helsinki. It was approved by the hospital's Institutional Review Board.

Results

Of the 283 patient charts gathered from March 2010 to March 2013, 104 fulfilled the inclusion criteria.

Majority of patients belong to the elderly group (mean age of 58.9 ± 11.9), mostly female (60%), obese (67%), and with long standing diabetes (mean duration of 9.0 ± 6.3 years), with an elevated baseline HbA1c of $10.1 \pm 2.1\%$ (Table I). The most frequently used medication prior to consultation was metformin (68%) and sulfonylurea (42%), while only a small percentage was already on insulin (18%). Majority (54%) was on triple drug therapy, 30% on two oral medications, and 17% on combination insulin and oral medication.

Hypertension and chronic kidney disease were the most common comorbid conditions seen in the patients at 54% and 35%, respectively.

At the beginning of the observation period, 85 patients were on oral medications,⁹ on combination of basal insulin and oral agents (Regimen A), and 10 on basal-bolus with or without oral agents (Regimen B) (Table II).

Looking at the group that started on purely oral medications, eight ended up on Regimen A (addition of basal insulin), twelve progressed to Regimen B (addition of basal-bolus insulin), two ended with Regimen C (addition of premixed 70/30 TID or premixed 70/30 BID with pre-lunch bolus), 52 ended with Regimen D (addition of Premix 70/30 BID and bolus TID), 11 were on Regimen E at the end of the observation period (addition of premixed 70/30 BID, bolus TID, and basal OD).

Tracing the clinical course of the nine patients who began with Regimen A (basal with oral), majority ended on Regimen B (addition of bolus TID), two on Regimen D (removal of basal, addition of premixed 70/30 BID and bolus TID), one on Regimen E (addition of premixed 70/30, and bolus TID).

Examining the group that was already on Regimen B (basal OD with bolus TID with or without oral medications), one progressed to Regimen C (shifted to premixed aspart 70/30 or lispro 75/25 TID or premixed aspart 70/30 or lispro 75/25 BID with pre-lunch bolus OD), three ended with

Table I. Baseline characteristics of patients

Variable	Value
Study population (N)	104
Age (Years)	58.9 ± 11.9
Male: Female	42: 62
Body Mass Index (kg/m ²)	27.2 ± 4.45
Obese	70/104 (67%)
Duration of Diabetes (years)	9.0 ± 6.3
Baseline HbA1c (%)	10.1 ± 2.1
Medications	Frequency of Use
Biguanides	71 (68%)
Sulfonylurea	44 (42%)
DPP4-inhibitor	33 (32%)
Insulin	19 (18%)
Thiazolidinedione	5 (5%)
GLP 1 agonist	1 (0.01%)
Alpha glucosidase inhibitor	1 (0.01%)
Co-morbid conditions	Frequency
Hypertension	56 (54%)
Chronic Kidney Disease	36 (35%)
Dyslipidemia	22 (21%)
Ischemic Heart Disease	9 (9%)
Cerebrovascular Disease	4 (4%)
Chronic Liver Disease	3 (3%)

Of the 283 patient charts gathered, 104 were included in the study. This table summarizes the attributes of the patients in terms of demographics, medications used upon referral, and co-morbid conditions.

Table II. Clinical Course of Patients: Initial to Final Regimen

Initial Regimen	Ended on Regimen A	Ended on Regimen B	Ended on Regimen C	Ended on Regimen D	Ended on Regimen E
Oral (n=85)	8	12	2	52	11
Regimen A (n=9)	N/A	6	0	2	1
Regimen B (n=10)	N/A	N/A	1	3	6
Total	8	18	3	57	18

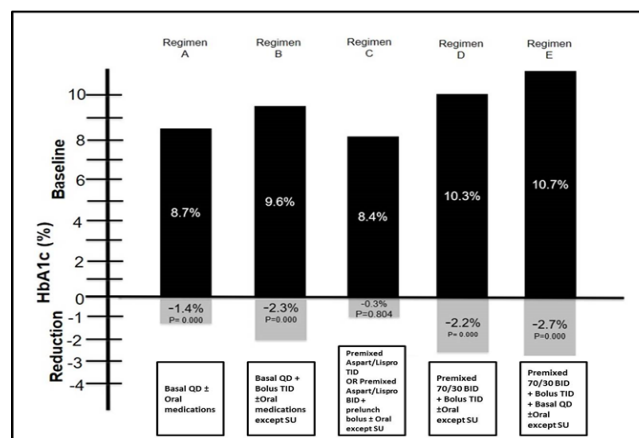
This table shows the number of patients that started on each regimen upon entry into the stepwise treatment and the number of patients on each regimen at the end of the 1 year observation period. The one with the most number of patients at the end was Regimen D (premix 70/30 BID + premeal bolus with lispro or aspart TID ± oral regimen except sulfonylurea).

*N/A not applicable

Regimen D (removal of basal, addition of premixed 70/30 BID), and six finished on Regimen E (addition of premixed 70/30 BID).

The trend seen in the course of treatment is that all patients necessitated increasing intensification of insulin treatment. Among those who started on oral medication, most ended up on Regimen D (Premix 70/30 BID + Bolus TID ± oral except SU). Those who started on Basal + oral ended up on Regimen B (basal OD + bolus TID ± oral except SU). Finally, those who started on the basal-bolus regimen ended up on the most intensive treatment, Regimen E (premixed 70/30 BID + bolus TID + basal OD ± oral except SU).

With the patients classified to the group of their final regimen, the mean change in HbA1c from beginning to end of the one year observation period was measured (Figure 2). Regimens A, B, D and E attained a statistically significant reduction, with the highest one reached by Regimen E at 2.7%. Regimen C exerted an HbA1c reduction of 0.3% (p value=0.81).

Figure 2. Baseline and mean change in HbA1c per regimen

This diagram shows the average baseline HbA1c of the patients per regimen at the beginning of the observation period, represented by the black bars. The mean change in HbA1c exerted by each regimen are depicted by the grey bars below the x-axis. Significant HbA1c reductions (p<0.05) were demonstrated by Regimens A, B, D and E. *SU-sulfonylurea

There were only 10 hypoglycemic events documented in the patient charts. Of these, six were probable symptomatic hypoglycemia, and four were documented symptomatic hypoglycemia. There was no documented severe hypoglycemia that required assistance by a lay caregiver or a healthcare professional.

The mean weight gain observed among the subjects was only 1.07 kg ±11.435 (p=0.335), which did not reach statistical significance, despite intensive insulin use (Table III)

Table III. Associated weight gain and events of hypoglycemia per regimen

Regimen	Mean Change in Weight in kg (p value)	Events of Hypoglycemia
A	-3.188 ± 5.099 (0.120)	0
B	-1.000 ± 3.204 (0.203)	3
C	-3.167 ± 3.547 (0.262)	0
D	2.107 ± 15.190 (0.304)	5
E	2.417 ± 4.797 (0.047)	2
Overall	1.070 ± 11.435 (0.335)	10

This table shows the common adverse events associated with the use of intensive insulin regimens, weight gain and events of hypoglycemia. Overall weight gain was not significant ($p < 0.05$), and events of hypoglycemia only 10.

Discussion

To summarize the key findings of this study, most of the patients included are obese, elderly, with longstanding diabetes. Most were already on triple drug therapy upon study entry. Majority of the patients attained good control on Regimen D. All regimens, except for Regimen C, exerted statistically significant HbA1c reduction. Hypoglycemia and weight gain were kept to a minimum.

A possible underlying mechanism linking all the prominent clinical features of obese, elderly, and long standing diabetes, is insulin resistance. This insulin resistance, coupled with decline in β -cell function, likely causes treatment failure on oral antidiabetic medications. This was seen in our patients' eventual need for insulin therapy, frequently of progressively increasing doses. This was demonstrated in the clinical course of the patients in this study, with majority attaining glycemic targets in the most intensive regimens.

Several studies have investigated the association between obesity and insulin resistance. Kahn et al. stated that insulin resistance in obesity and type 2 diabetes mellitus is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and skeletal muscles, and by impaired suppression of hepatic glucose output. These functional defects may be a result of impaired insulin signaling in the target tissues, and in addition, down regulation of the major insulin-responsive glucose transporter, GLUT4.²³ This decrease in GLUT4 is seen in adipocytes, whereas in skeletal muscles, although the levels are normal, defective glucose transport seems to be due to impaired translocation, docking, or fusion of GLUT4 containing vesicles with the plasma membrane¹⁷.

It is noteworthy that it is not only obesity per se, as

reflected by the BMI, that confers insulin resistance, but the intra-abdominal/visceral depots of fat that plays a more major role. A leading hypothesis for this is that intraabdominal adipocytes are more lipolytically active, which increases intraportal free fatty acid levels and flux, which might inhibit insulin clearance and promote insulin resistance by mechanisms which are still unclear. Hyperinsulinemia per se can cause insulin resistance by downregulating insulin receptors and desensitizing postreceptor pathways.^{18,19}

The aging process was described by Fink, et al. to be associated with the development of a glucose intolerance, which appears to be the consequence of peripheral insulin resistance. The mechanism behind this is a postreceptor defect in target tissue insulin action, which causes both a decrease in the maximal rate of peripheral glucose disposal and a rightward shift in the insulin action dose-response curve.²⁰

Long duration of diabetes increases insulin resistance. This translates to an increase in the following parameters over time : HbA1c, fasting, and postprandial blood glucose.²¹ The UKPDS showed that decline in beta cell function begins as early as 12 years before diagnosis and progresses throughout the disease course.¹

Several barriers to insulin initiation and treatment exist, both from patient and physician factors. The predominant reason is perceived risk of hypoglycemia, weight gain, lack of familiarity or experience with treatment, insulin being thought of as a last resort or end-stage therapy. Treatment inertia leads to increased length of time on oral antidiabetic drugs (OADs) with high glycemic burden before initiation of insulin therapy.^{22,23} Consequently, the number and extent of diabetes related complications are extensive in such a population. The treatment algorithm in this specialty clinic offers a treatment strategy option to non specialists in order to overcome the inertia to insulin use.

Two of the principles adhered to in this clinic were early insulinization, deemed by several authors to preserve β -cell function,²⁴ and incremental use of insulin, based on the premise that the natural evolution of diabetes mellitus type 2 is progressive β -cell dysfunction and increasing insulin resistance.²⁴

Early initiation of insulin has various benefits, including overcoming glucotoxic effects of hyperglycemia, thereby facilitating β -cell rest and preserving beta cell mass and function, while also improving insulin sensitivity. Optimal glycemic control is achieved through disease remission. In addition to this, insulin has anti-inflammatory and antioxidant properties that may help protect against endothelial dysfunction and damage resulting in vascular disease. Early treatment with insulin thereby results in earlier achievement of good glycemic control, and long term protection of end organs via "metabolic memory" as evidenced by UKPDS.²⁵⁻²⁷ This is the rationale behind setting a low threshold for initiating insulin treatment, and aggressive stepping up to a more intensive regimen, using an HbA1c of $\geq 8\%$, in this specialty clinic.

Regimen D emerged as the final regimen used by majority of patients, that is, the regimen where most attained HbA1c target. Among the regimens preceding this is the basal bolus regimen (Regimen B), recognized as the most intensive insulin treatment given via multiple daily injections to achieve glycemic targets, short of a continuous subcutaneous insulin infusion or the insulin pump. However, there still remains about 30% of those using the basal-bolus regimen who do not achieve good control.²⁸ Since the use of insulin pump is not yet feasible in our local setting because of the high cost, there is a need for alternative regimens such as Regimens D and E. The study done by Laplano et al. in 2012 showed that the use of Regimen D resulted in attainment of HbA1c target (32% reduction from baseline) in 6.7 months, and this good control was sustained for more than five years in a proportion of patients. The study stated that the rationale behind the success of Regimen D is that it mimics the biphasic nature of insulin secretion. Physiologically, basal insulin secretion accounts for 50% of the total insulin secreted in a 24-hour period, and the remainder is secreted in response to prandial glucose excursions. This prandial secretion is rapid, and increases over fivefold over baseline, reaching a peak within 60 minutes. With a constant rate of intravenous glucose infusion, an initial biphasic secretory response is observed- a rapid first phase release of pre-formed insulin which peaks in three to five minutes, followed by a second phase release of newly formed insulin beginning at two minutes and continues to increase slowly for at least 60 minutes or until the stimulus stops. Translating this into the components of Regimen D, the short-acting regular human insulin which has onset of 30 minutes to one hour and peaks at two to four hours reduces the peak of postprandial glucose rise, while the intermediate acting NPH insulin which has a peak of eight to six hours, and duration of 12-16 hours controls basal glycemia due to hepatic glucose output. This premixed combination given twice a day approximates the slower sustained second phase of post-prandial insulin secretion as well as basal insulin requirement, providing control for over 24 hours. By adding insulin lispro or aspart, which have an onset of action five to 15 minutes given thrice daily, the rapid first phase of post-prandial insulin secretion is also simulated.⁷

Intensive insulin treatment increases the risk of hypoglycemia, specifically in patients who have longstanding diabetes, cognitive impairment, and hypoglycemia unawareness. Severe hypoglycemia has been linked to cardiovascular events.²⁹ This is well recognized, and prevented in this clinic through the employment of automatic snacking, that is, incorporation of snacks two hours after main meals even in the absence of hunger. This strategy was demonstrated to offset hypoglycemic events in previous studies by promoting compliance to insulin treatment, ultimately enabling attainment of good control.^{7,16} Albeit the possibility of underreporting, there were only a few recorded events of hypoglycemia in this study, none of which were severe.

Some weight gain was noted, as expected with intensive insulin treatment, the highest seen in the most intensive Regimen E at 2.417 ± 4.797 kg (0.047). Nonetheless, overall weight gain was not statistically significant (Table III). In the UKPDS, patients in the intensive-treatment group gained an average of 4.0 kg compared with patients in the conventional treatment group.³⁰ The possible reason for this modest, statistically insignificant weight gain is the strong patient education about diet intervention and the need for exercise as important aspects of diabetes management at initial consultation, and reinforced during every visit, with due monitoring of weight. In addition to this, information about possible weight gain secondary to insulin use is readily given to the patient, possibly serving as incentive to adhere to recommended lifestyle change. In a review by Russel-Jones, diet and exercise are strong strategies utilized to limit insulin-associated weight gain through its effect of increasing patients' sensitivity to insulin. In addition to this, the use of insulin-sensitizing drugs, such as metformin, is another way to minimize insulin-associated weight gain.³¹ Metformin was used in majority of the patients in this study (68%).

The benefits of early, aggressive control of diabetes mellitus type 2 lie in the prevention of complications. Challenges to treatment is a reality that clinicians and patients face everyday. Some of the strategies to circumvent these obstacles include robust education on lifestyle change, creation of guides, algorithms and protocols for care providers, such as the one described in this study.

The limitations of this study are related the retrospective design and limited number of patients. A prospective study, with a bigger patient population, comparing the different insulin regimens would eliminate the selection and information bias, and would be worthwhile to explore.

Conclusion

The stepwise insulin combinations treatment algorithm utilized in this clinic appears to be a feasible tool in diabetes management in that it exerted significant HbA1c reduction towards desirable levels among the patient population, and resulted in minimal occurrences of hypoglycemia as well as statistically insignificant weight gain. These are attributed to automatic snacking two hours after main meals, and proper education about diet and exercise.

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