Change in HbA1c Among Filipino Diabetic Patients who Shifted from Multiple Daily Injection to Continuous Subcutaneous Insulin Infusion: A Retrospective Cohort Study

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Abstract

Introduction: Insulin delivered by multiple daily injection (MDI), for a time, has been considered to be the most physiologic among the different insulin regimen. Among patients on MDI, there is still a significant proportion who remains uncontrolled. Continuous subcutaneous insulin infusion (CSII) or insulin pump has been shown to benefit some patients who are still uncontrolled despite intensive insulin therapy with MDI. Currently, there is little information on the use of insulin pump in the Philippines. The researchers aim to determine the change in HbA1c and the proportion of patients with HbA1c of <8% after shifting from MDI to CSII. To correlate the change in HbA1c with age and baseline HbA1c. To compare the change in HbA1c between gender, type of diabetes and type of bolus regimen.

Methods: This is a retrospective cohort analytical study of 33 adult patients with type 1 or type 2 diabetes mellitus (DM), switched from MDI to insulin pump. Chart review was done to obtain data on age, gender, type of bolus, baseline HbA1c and HbA1c six to twelve months after switching insulin pump initiation. The change in HbA1c was correlated with baseline HbA1c and age. Mean change in HbA1c was also compared between gender, type of bolus and type of diabetes.

Results: Mean HbA1c prior to switching to insulin pump was 10±1.7. The HbA1c reduction was 1.86±1.6 (p<0.001, CI 1.38-2.34), resulting to a mean final A1c of 8.1±1.2 after CSII initiation. Seventeen out of 33 patients (52%) achieved an average HBA1c of <8%. A positive correlation was observed between HBA1c reduction and baseline HbA1c (r =0.738, p<0.001) but not with age (r = -0.002, p=0.99). There was no significant difference in the HbA1c reduction between male and female (p=0.353), Type 1 DM and Type 2 DM (p=0.133), and those that used fixed bolus vs bolus calculator (p=0.559). The reduction in A1c remains significant when analyzed as individual subgroups: 2.1±2.3 (p=0.001) in males; 1.6±1.0 (p<0.001) in females; 1.5±1.6 (p=0.001) in type 1; 2.3±1.6 (p<0.001) in type 2; 2.1±1.5 (p<0.001) in bolus calculator, and 1.7±1.8 (p<0.001) in fixed bolus group.

Conclusion: There is significant reduction in HbA1c among this cohort of Filipino diabetic patients after switching from MDI to CSII. While majority of patients had >1% reduction, achieving an ideal goal of <7% remains to be a challenge. Greater HbA1c reduction are seen in patients with higher baseline HbA1c. There is no significant difference in the reduction in HbA1c with respect to gender, type of diabetes and type of bolus used.

Keywords: hb1ac, multiple daily injection, continuous subcutaneous insulin infusion, insulin pump, diabetes mellitus

Introduction

Insulin is the cornerstone treatment for type 1 diabetes mellitus (DM). With progressive beta cell dysfunction many patients with type 2 DM also would later on need insulin as part of their armamentarium. For a time, multiple daily injection (MDI), particularly basal-bolus, was considered to be the most physiologic among the different insulin regimen. This intensified insulin treatment requires multiple injections: a long acting insulin and a short or rapid acting timed with meals. This regimen was shown to be effective in improving glycemic control in Filipinos.[1] However, there is still a significant number of patients who remain poorly controlled on MDI.

Another form of insulin delivery is continuous insulin infusion (CSII), or insulin pump therapy. The insulin pump is a portable device that delivers rapid acting insulin continuously through a cannula inserted subcutaneously. It can be programmed to deliver basal insulin at different rates at different times of the day, with increments of as little as 0.01units/hr. Bolus insulin can be given to cover carbohydrate intake or correct hyperglycemia. The site is changed every few days, allowing less injections. CSII has been recommended for patients with type 1 DM who have not achieved their A1c goal, or those who experiences

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severe hypoglycemia and high glucose variability. It is may also be considered for motivated patients with type 2 DM who fails to achieve optimal control on intensive insulin therapy.[2]

For both type 1 DM and type 2 DM patients, several studies have reported better HBA1c reduction among patients on CSII compared to MDI, without associated increase in hypoglycemia risk.[3-7] There are also reports of improvement in glucometrics other than HbA1c such as time spent in target range blood sugar range.[8,9] More consistently, studies have shown improvement in treatment satisfaction and quality of life measures among patients on CSII.[10-12] Better treatment satisfaction has been shown to have positive correlation with patient's compliance.[13,14] This in turn may also result to improvement in glycemic control.[15,16]

Currently, there are no available data on the use of CSII in the Philippines. Given the significantly greater expense of insulin pump and the lack of insurance coverage for its use in the Philippines; it is important to look at efficacy of insulin pump in achieving glycemic control among Filipino patients. This study aims to determine the glycemic control of Filipino diabetic patients who shifted from MDI to CSII; describing their demographic characteristics, disease profile and the change in HbA1c level.

Methods

This is a retrospective cohort analytical study of patients with diabetes mellitus on continuous subcutaneous insulin infusion seen at various endocrinologists' private clinic.

The total number of patients who have been started on insulin pump in the Philippines since 2006 was obtained from Medtronic Philippines. Names of the patients remained anonymous. The attending physicians who agreed to participate reviewed their patient's medical record. Data gathered include age, gender, weight, type of DM, use of bolus calculator vs fixed bolus, total daily insulin dose, baseline HbA1c, and HbA1c six to twelve months following insulin pump initiation. Recruitment and data collection were done within three months. Data gathered are then included in the analysis by the investigators. Inclusion criteria were as follows: patients at least 19 yrs old with either type 1 DM or type 2 DM, who were previously on MDI, switched to insulin pump for at least six months. Only patients with a record of HbA1c before pump initiation and six to twelve months after were included in the study. Patients who were lost to follow-up or have discontinued using their insulin pump were excluded.

At alpha=0.10, Beta=0.20, and assumed difference in the baseline and follow-up HbA1c (%) of 0.6, at least 32 subjects are needed. The assumed difference in the baseline and follow-up HbA1c (%) was based from the study by Sanjeev Mehta, et al. "Changes in HbA1c and Weight Following Transition to Continuous Subcutaneous Insulin Infusion Therapy in Adults with Type 1 Diabetes" published at Journal of Diabetes Science and Technology, 2017.

Data was encoded and tallied using Microsoft Excel and XLStat. Descriptive statistics was generated for all variables. For nominal data frequencies and percentages were determined; for numerical data, mean±SD were generated. Analysis of the different variables was done using the following test statistics: Paired t-test for change in HbA1c and Mann Whitney U test was used for comparing two categorical groups with numerical data. Pearson Correlation was used to determine correlation between two numerical variables (age and baseline HbA1c with HbA1c reduction).

Results

Overall 134 patients have been on insulin pump since 2006. After applying the exclusion criteria, 33 patients were included in the analysis. (Figure 1)

Patient's demographic distribution are shown in Table I. Baseline HBA1c ranged from 6.7% to 12.8%, with a mean of 10% ±1.7. Type 2 DM group had a significantly higher mean baseline A1c compared to type 1 DM subjects. Data on weight, TDDI and occurrence of hypoglycemia were limited. The insulin dose on CSII were mainly determined and adjusted by the discretion of the attending physician.

The mean HbA1c six to twelve months after CSII initiation was 8.1%± 1.2. A mean HbA1c reduction of 1.86% ±1.6 from baseline (p<0.001, CI 1.38-2.34). Of the 33 patients, majority (79%) had least one percent reduction, while there were three patients who had a rise in HBA1c. Trend of change in HbA1c is shown in Figure 2. Seventeen patients (52%) achieved an average HBA1c of <8%, three of which were <7%. Among the four patients with HbA1c <8% at baseline, one patient had a rise of 1.4%, two had no significant change, and one had significant improvement with a reduction of 1.7%.

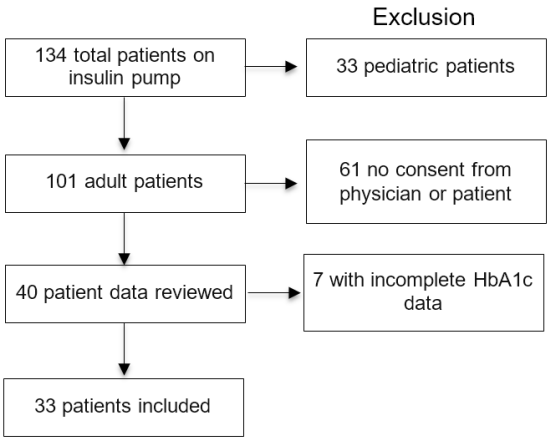

Figure 1. Study population

Table I. Demographic, clinical and treatment factors

Variable	Measurement	Percentage (%)
Age (yrs)±SD ; Range (19-74)	41 ± 18.4	
Gender		
Male	16	48.5
Female	17	51.5
DM Type		
Type 1	18	54.5
Type 2	15	45.5
Bolus Type		
Fixed	19	61.3
Bolus calculator	12	38.7
No data	2	
Baseline HBa1c		
HbA1c <8%	4	12
HbA1c ≥8%	29	88
HbA1c range (%)	6.7 to 12.8	
Mean HbA1c (%)±SD	10.0 ±1.7	

The baseline HbA1c were similar between male and female, and those that used the bolus calculator vs fixed bolus. Patients with type 2 DM had higher HbA1c compared to patients with type 1 DM prior to switching to CSII (p=.032).

The HbA1c reduction remains significant when analyzed in subgroups (Figure 3). There was no significant difference in HbA1c reduction between male and female, type 1 DM and type 2 DM, and those that used fixed bolus vs bolus calculator (Figure 4). Greater HBA1c reduction were observed in patients with higher baseline HBa1c (r=0.738, p<0.00, Figure 5). No correlation was found between age and degree of HBa1c reduction (r=-0.002, p=0.99, Figure 6).

Discussion

Management of diabetes continues to be a challenge. The National Health and Nutrition Examination Survey data in the US showed that over the past decade, the proportion of patients achieving glycemic control targets has not improved.[17] A study in 2008 done in our local setting, also showed inadequate control of blood glucose among Filipinos with type 2 DM.[18] The significance of glycemic control is well established in that, near-normal glycemic control delay progression of microvascular and macrovascular complications in patients with type 1 DM.[19, 20] There is also significant reduction in myocardial infarction and all-cause mortality among patients with type 2 DM.[21]

Significant reduction in HbA1c was seen in our cohort of patients who switched from MDI to CSII. The degree of reduction was positively correlated with baseline HbA1c. There was no significant difference in the HbA1c reduction between male and female, type 1 DM and type 2 DM, and those that used fixed bolus vs bolus calculator. The reduction

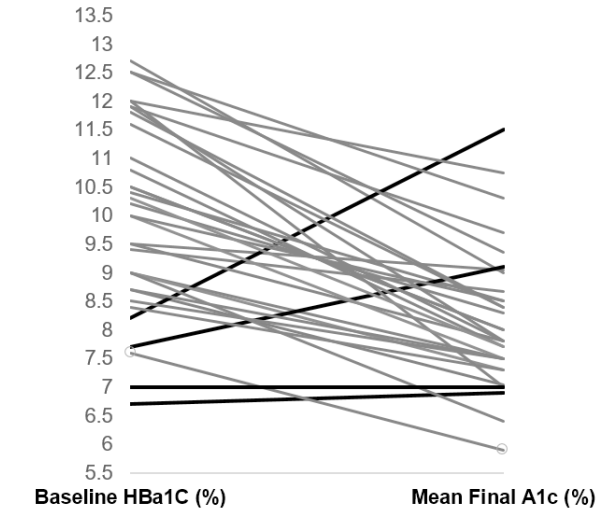

Figure 2. Trend of HbA1c change among individual patients

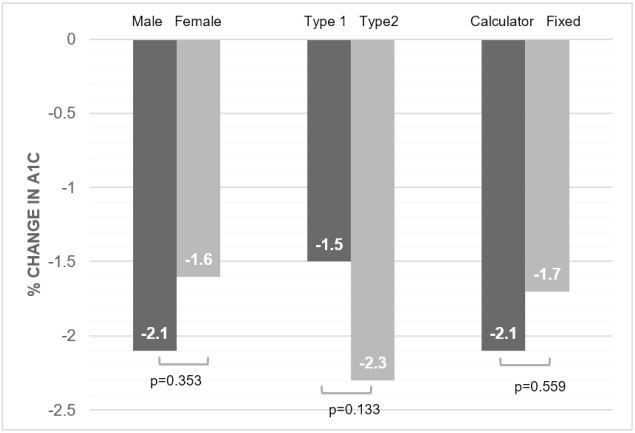

Figure 3. Difference in the change in HbA1c between gender, type of diabetes and type of insulin bolus

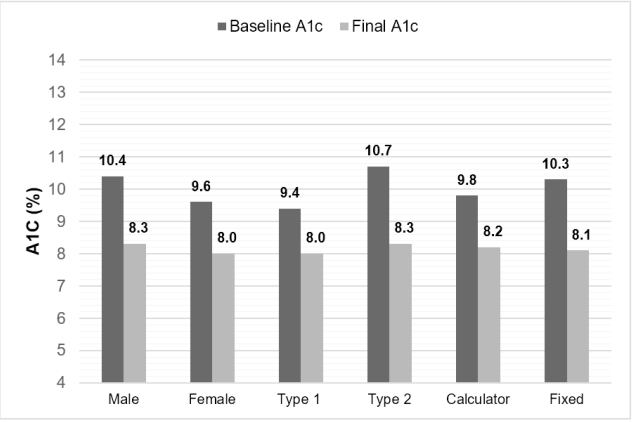

Figure 4. Before and after continuous subcutaneous insulin infusion according to individual subgroups

in A1c remains significant when analyzed as individual subgroups.

Several randomized control trials (RCTs) and meta-analysis has shown reduction in A1c of 0.3-0.8% among adults with type 1 DM switched from MDI to CSII.[3,4] Observational

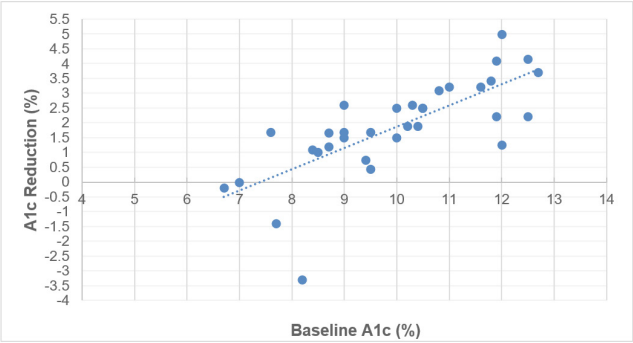

Figure 5. Correlation of baseline HBA1c and HbA1c reduction

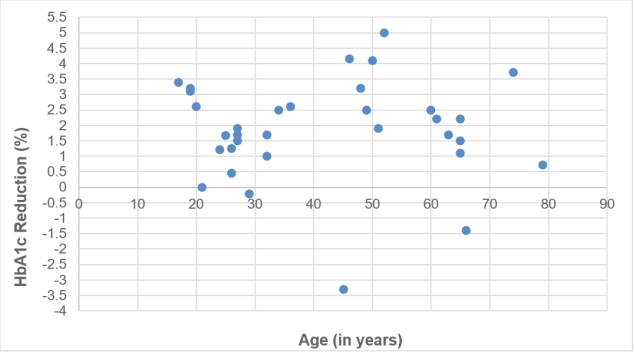

Figure 6. Correlation of age and HbA1c reduction

studies have shown an improvement ranging from 0.7-1.2%.[22,23]

Among patients type 2 DM, uncontrolled studies on patients with type 2 DM have also reported improvement in glycemic control, with A1c reduction ranging from 0.5% to 2%.[24-26] However, results from RCTs have been inconsistent; with earlier ones failing to show significant improvement.[29-31] On the contrary, the more recent multi-center RCT (Opt2mize study) reported superior reduction of 1.1% from baseline among patients on CSII patients compared to 0.4% among those on MDI. This study only included patients with baseline A1c between 8.0-10.0%, who demonstrated adherence during a two-month run-in period. The greater HbA1c reduction seen in observational studies and the Opt2mize study was thought to be due to better patient inclusion criteria in the clinical setting.[2, 32]

Our study showed an HbA1c reduction (1.86% ±1.6) more consistent with that seen in observational studies. A possible reason for this is that Filipino patients considered for CSII have higher baseline HbA1c. Considering the cost and lack of insurance coverage, physicians are likely to be more selective in recommending patients for such treatment modality. This higher HbA1c reduction seen in our study supports the idea that candidates who are carefully selected may get more benefit from CSII.

The American Diabetes Association recommends a HbA1c goal <7% for most adults, or <6.5% for selected patients where it can be achieved without significant hypoglycemia or adverse effects.[33] In a local survey by Jimeno et al., only 15% of Filipino patients with type 2 diabetes had an HbA1c of <7%.[18]

Several studies in the US and Europe evaluating CSII use, resulted to a mean final HBA1c 7.3-8.2%.[34] In contrast, a study done in South Korea had a lower mean final HbA1c of 5.0%±0.9.[7] However, patients included this study had a mean baseline of 7.9%±1.9 and were on OAD or basal insulin as their previous regimen.

In the Opt2mize study, 55% of subjects achieved HBA1c < 8% compared to 28% of patients on MDI.[32] Our study also showed a similar proportion, with over half of the patients with mean final HbA1C of <8%.

Despite the significant change in HbA1c with majority of patients having >1% reduction, only a few had a mean final HbA1c of <7%. Similar to the US and European studies, our patients had poor control at baseline despite intensified treatment with MDI. This suggests that despite use of CSII, achieving a more stringent goal of <6.5-7.0% continues to be a challenge for patients with more advanced disease.

Evidence on predictors of success in achieving glycemic goal are limited. What has been consistently shown is that patients with worse control are likely to have greater A1c reduction.[2, 23, 35] In a study by Pickup et al., the improvement in A1c directly correlated with both HbA1c and glucose variability prior to CSII.[23] Retnakaran et al., using a model derived from their data, predicts an additional reduction of 0.65% with CSII compared to MDI for a baseline A1c of 10%, but no additional A1c lowering benefit if baseline A1c were 6.5%.[35] Findings in our study are consistent with previous observations. Use of CSII appears to be particularly beneficial in patients with poor glycemic control.

The baseline HbA1c in our study tend to be higher among patients with type 2 DM. Physicians may have a higher HbA1c threshold before considering CSII in type 2 DM compared to those with type 1 DM. Although not statistically significant, the A1c reduction was greater among the patients with type 2 DM, likely due to their higher baseline A1c. HbA1c reduction is significant whether in type 1 or type 2.

We did not find any correlation between age and degree of HBA1c reduction. A study Matejko et al. also found no differences in glycemic control achieved with CSII treatment in type 1 DM patients over 50 years old vs. younger subjects.[36] In another study done by the same group, worse glycemic control was seen in the younger patients on CSII. However, this was thought to be possibly related to age-dependent behaviors in the young diabetic group. They found that these patients had less frequent use of advanced pump functions and self-monitoring blood

glucose (SMBG).[37] Therefore, age alone should not be the main factor in choosing a candidate for CSII. More important to consider than age itself is patient likelihood of adherence. History of missed appointments and mental illness that are likely to cause poor adherence have been reported to have worse outcomes. In Opt2mize study, patients with mild cognitive impairment still benefited from CSII use. Reznik et al., concluded in another study that cognitive and mood evaluation tools can help identify patients who may need personalized training programs or nurse's assistance for CSII utilization.[32]

Bolus calculator is built in feature of insulin pumps. It determines the dose of insulin given based on the amount of carbohydrate or their capillary blood glucose the patient enters. Whereas fixed bolus is entered by the patient, usually based on a pre-determined dose. Several studies found that among patients with type 1 DM, use of bolus calculator was associated with improved glycemic control and less need for treatment for hypoglycemia or correction of hyperglycemia.[38-40] For patients with type 2 DM, the evidence on benefit of bolus calculator are inconsistent. Leuning et al. reported no difference in HbA1C improvement between the group that use of frequent bolus adjustment incorporating carbohydrate counting and those that use manual bolus.[41] The Opt2mise study also reports good glycemic control in most of their patients who were on fixed bolus regimen.[32] Some studies have shown beneficial outcomes including reduced hypoglycemia, post-prandial glucose and decrease need for correction insulin.[2] Using the bolus calculator in the Philippine setting may be challenging. Nutrition information and labeling other than on pre-packaged food is limited compared to Western countries.[42] In our study, the HbA1c reduction were similar for both groups using fixed bolus or bolus calculator. Guidelines on CSII use encourage use of bolus calculators and determining individualized insulin-CHO ratio and insulin sensitivity factor (ISF). However, its use can also be beneficial even in patients who are unable to do more complex regimen that requires carbohydrate counting.

A major limitation in our study is its retrospective nature. Data on duration of diabetes, hypoglycemia, blood glucose monitoring frequency, and total daily dose of insulin are lacking. We suggest that future prospective studies with a control group be done to better identify more variables that may help predict successful glycemic control. Future studies may incorporate use of continuous glucose monitoring to determine effect on glucose variability and time spent in target range. A study on change in treatment satisfaction in patients switched to CSII, would also help in weighing the cost to benefit ratio. Another limitation is the small sample size. There are only a few number patients on insulin pump in the Philippines, it would be ideal to include more patients in a multi-center prospective study.

Conclusion

There is significant reduction in HbA1c among this cohort of Filipino diabetic patients who switched from MDI to CSII. Majority of patients had >1% reduction, with over half of the patients having a final HbA1c <8%. Achieving an ideal goal of <7% however, remains to be a challenge. The degree of HbA1c reduction is positively correlated with baseline HbA1c. This makes CSII particularly beneficial in patients with worse glycemic control. Age is not a significant determinant of improvement in HbA1c with use of CSII. There is no significant difference in the reduction in HbA1c with respect to gender, type of diabetes and type of bolus used.

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