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ORIGINAL ARTICLE

Insulin initiation for patients with poorly controlled type 2 diabetes mellitus

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Abstract

Background: We examined the initiation of insulin therapy in patients with poorly controlled type 2 diabetes mellitus (T2DM), analyzed their glycemic responses, and compared patient profiles based on glycemic outcomes.

Methods: Patients with T2DM initiated on insulin therapy were retrospectively analyzed. Data were collected from endocrinology clinic before and 3 and 6 months after insulin initiation. The primary outcome was hemoglobin A1c (HbA1c) level 6 months after commencing insulin treatment. Secondary outcomes included HbA1c levels at 3 months after insulin treatment and fasting blood glucose levels at 3 and 6 months after treatment. We analyzed the effects of insulin initiation and categorized patients based on their 6-month HbA1c levels: below the median of 7.8% (better response) and above 7.8% (worse response). Additionally, we evaluated patients based on HbA1c changes at 6 months, with greater or lesser changes defined by the cohort's median change of –1.4%.

Results: Insulin therapy significantly reduced HbA1c (from 9.8% to 8.2%) and fasting blood glucose levels (from 221.4 to 147.2 mg/dL) within 3 months. After 6 months, HbA1c and fasting blood glucose levels decreased by 2.1% (9.8%-7.7%) and 77.2 mg/dL (221.4-144.2 mg/dL), respectively. Patients who responded better to insulin treatment showed lower fasting blood glucose levels by 6 months after insulin initiation and lower HbA1c levels as soon as 3 months after initiation. Patients with higher baseline glycemic profiles experienced significantly greater HbA1c reductions at 6 months post-treatment.

Conclusion: Insulin therapy significantly improved glycemic control in patients with T2DM within 3 months after initiation. Patients with higher baseline glycemic profiles experienced greater responses to insulin therapy.

Keywords: Insulin naive; Insulin therapy; Type 2 diabetes mellitus

1. INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is rising and posing a global health challenge. Diabetes mellitus is linked to metabolic disorders that elevate cardiovascular risk.[1] Diabetes management requires an individualized approach and ongoing monitoring, incorporating dietary modifications, physical activity, and medications. Most patients need both lifestyle changes and pharmacological therapy and treatment plans evolve as the disease progresses.

Insulin therapy is a cornerstone of diabetes management due to its effectiveness in lowering glucose levels and reducing the risk of complications.[2] Insulin regimens are highly personalized, varying between patients and healthcare providers. However, data comparing different insulin regimens are limited. Additionally, some studies suggest that there are no significant differences in glycemic control or hypoglycemic complications among the regimens.[3] This study investigated the effects of initiating insulin therapy in patients with poorly controlled T2DM.

2. METHODS

2.1. Study population

We retrospectively analyzed data from an endocrinology outpatient clinic at a single tertiary medical center in Taiwan, collected between November 2020 and December 2020. The inclusion criteria were patients with hemoglobin A1c (HbA1c) levels >7%, who visited the clinic, and who were scheduled for their first insulin injections. Patients who refused insulin therapy, had prior insulin use, or declined data collection were excluded. During the study period, 71 patients with T2DM exhibiting HbA1c levels of >7% who received their first insulin injection were included. Of the 71 patients, 36 were women and 35 were men, with an average age of 60.0 ± 14.5 years; the mean body mass index (BMI) was 26.6 ± 5.2, and the average duration of T2DM was 10.0 ± 7.1 years. The baseline fasting blood glucose and HbA1c levels were recorded before insulin initiation. These levels were then measured at 3-month intervals for at least 6 months after the initiation of insulin therapy. The primary outcome was HbA1c level at least 6 months after commencing insulin treatment. Secondary outcomes included HbA1c levels at 3 months after insulin treatment and fasting blood glucose levels at 3 and 6 months after treatment.

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2.2. Data analysis

Data analysis was conducted in three distinct parts to comprehensively evaluate the impact of insulin treatment and explore variations in patient responses: (1) evaluating changes in glycemic profiles after insulin initiation; (2) comparing patient profiles based on higher or lower absolute HbA1c levels after insulin treatment; and (3) comparing patient profiles based on greater or lesser HbA1c reductions after insulin treatment. In the first part of our analysis, we compared the HbA1c levels of patients across the cohort before insulin initiation as well as at 3 and 6 months post-treatment. In the second part, the patients were divided into two groups: group 1 included those whose HbA1c levels below the cohort's median at 6 months post-treatment, while group 2 consisted of patients whose HbA1c levels were higher than the median. Age, sex, BMI, duration of diabetes history, fasting blood glucose and HbA1c levels at baseline and 3 and 6 months post-treatment were analyzed. In the third section, we divided the same set of patients into two groups: group A included individuals who demonstrated whose HbA1c reduction at 6 months post-treatment exceeded the cohort's median change, while group B included patients with reductions lower than the median.

Paired *t* tests were used to compare patients' HbA1c levels before and after insulin initiation. Independent *t* tests were used to compare mean age, BMI, duration of diabetes history, baseline fasting blood glucose, baseline HbA1c, and fasting blood glucose and HbA1c levels at 3 and 6 months post-treatment. Chi-square tests were used to assess sex-related differences between groups, with statistical significance set at $p < 0.005$. This comprehensive methodology aimed to evaluate the effects of insulin treatment on HbA1c levels in a diverse cohort of patients with T2DM and analyze variations in patient responses based on multiple factors.

3. RESULTS

3.1. Effects of insulin therapy

A total of 71 patients were enrolled in this study (Table 1). Eight patients had missing data or missed the 3-month follow-up, while 21 patients had missing data or did not attend the 6-month follow-up (Table 2).

Significant decreases in HbA1c levels were observed after 3 and 6 months of insulin therapy, decreasing by 1.61% and 2.1%, respectively. Likewise, significant decreases in fasting blood glucose levels were noted after 3 and 6 months of insulin therapy, with reductions of 74.2 and 77.2 mg/dL, respectively.

3.2. Comparison of patients that responded better and worse to insulin treatment

Of the initial 71 patients, HbA1c data at the 6-month follow-up were available for five; in this group, the median HbA1c level after 6 months of insulin treatment was 7.8%. Patients were divided into groups 1 and 2 (Table 3): group 1 comprised 27 patients with HbA1c levels ≤7.8% after 6 months of treatment, and group 2 comprised 23 patients with HbA1c levels >7.8%. The remaining 21 patients had missing data or did not attend the 6-month follow-up visit.

Significant differences were observed between the two groups in fasting blood glucose levels at 6 months post-treatment and in HbA1c levels at 3 and 6 months post-treatment. Group 1 patients had an average fasting blood glucose level of 120.6 ± 37.4 mg/dL after 6 months of treatment and HbA1c levels of 7.3 ± 1.6% and 6.7 ± 1.2% after 3 and 6 months of treatment, respectively. Group 2 patients had an average fasting blood glucose level of 166.4 ± 53.4 mg/dL after 6 months of treatment and HbA1c levels of 8.8 ± 1.3% and 9.0 ± 1.5% after 3 and 6 months of treatment, respectively. There were no significant differences in age, sex, BMI, duration of diabetes history, or baseline fasting blood glucose and HbA1c levels before treatment between the two groups. Although group 1 had lower fasting blood glucose levels at 3 months than group 2, the difference was not statistically significant.

3.3. Comparison of patients that responded more and less drastically to insulin treatment

Among the 50 patients, the median change in HbA1c levels after 6 months of insulin treatment compared with baseline levels was –1.4%. Patients were divided into groups A and B (Table 4): group A included 25 patients with HbA1c reductions ≥1.4%, while group B included 25 patients with reductions <1.4%.

Significant differences were observed between the groups in baseline fasting blood glucose and HbA1c levels before insulin initiation as well as in HbA1c levels after 6 months of treatment. Group A patients had an average baseline fasting blood glucose level of 271.7 ± 68.5 mg/dL and HbA1c level of 10.7 ± 1.9% before insulin initiation and an average HbA1c level of 7.1 ± 1.2% after 6 months of treatment. Before insulin initiation, group B patients had an average baseline fasting blood glucose level of 182.5 ± 42.9 mg/dL and HbA1c level of 8.6 ± 1.0%. After 6 months of treatment, their average HbA1c level was 8.5 ± 1.4%. No significant differences were observed in age, sex, BMI, or duration of diabetes between the two patient groups. Additionally, fasting blood glucose levels at 3 and 6 months and HbA1c levels at 3 months post-treatment showed no significant differences.

Table 1

Demography of the study population

Characteristics	Mean
N (persons)	71
Age (y)	60.0 ± 14.5
Sex (male:female)	36:35
BMI (kg/m^2)	26.6 ± 5.2
Duration (y)	10.0 ± 7.1
Baseline fasting glucose (mg/dL)	225.4 ± 75.3
Baseline glycated hemoglobin (HbA1c) (%)	9.8 ± 1.8

BMI = body mass index; HbA1c = hemoglobin A1c.

4. DISCUSSION

Our study provides valuable insights into patient responses to insulin therapy. It included patients with long-standing T2DM who had difficulty achieving adequate blood sugar or HbA1c control through lifestyle changes or oral hypoglycemic agents. Herein, we present first-hand clinical experience to guide physicians in initiating insulin therapy. We also examined the variations in patient responses to insulin therapy, shedding light on those who responded more favorably and faced greater challenges during treatment.

Insulin therapy effectively lowered HbA1c levels, with significant reductions observed within 3 months of initiation and sustained for at least 6 months. The same positive effect of insulin therapy was evident in the reduction in fasting blood glucose levels. Physicians can anticipate a significant reduction in HbA1c levels after initiating insulin therapy in patients with T2DM who struggle to control disease progression with lifestyle modifications and oral hypoglycemic agents alone. In addition, owing to the increased prevalence of blood glucose testing at

Table 2

Changes in glycated HbA1c and blood glucose levels after 3 and 6 mo of insulin treatment

Blood glucose variables	Mean	Changes	N	*p*
Baseline HbA1c (%)	9.8		71	
HbA1c after 3 mo (%)	8.2	−1.6	63	<0.001
HbA1c after 6 mo (%)	7.7	−2.1	50	<0.001
Baseline blood glucose (mg/dL)	221.4		71	
Blood glucose after 3 mo (mg/dL)	147.2	−74.2	63	<0.001
Blood glucose after 6 mo (mg/dL)	144.2	−77.2	50	<0.001

HbA1c = hemoglobin A1c.

Table 3

Comparison of patients that responded better and worse to insulin treatment

Characteristics	Group 1 (better response)	Group 2 (worse response)	*p*
Age (y)	58.7	64.2	0.178
Sex (male:female)	14:13	11:12	0.777
BMI (kg/m^2)	26.3	27.2	0.613
Duration (y)	8.6	10.5	0.320
Baseline fasting glucose (mg/dL)	224.9	232.2	0.730
Baseline glycated hemoglobin (HbA1c) (%)	9.3	10.1	0.166
Fasting glucose after 3 mo of treatment (mg/dL)	132.3	147.1	0.200
Fasting glucose after 6 mo of treatment (mg/dL)	120.6	166.4	<0.001
HbA1c after 3 mo of treatment (%)	7.3	8.8	<0.001
HbA1c after 6 mo of treatment (%)	6.7	9.0	<0.001

Group 1: Patients with HbA1c levels ≤7.8% after 6 mo of treatment. Group 2: Patients with HbA1c levels >7.8% after 6 mo of treatment.
BMI = body mass index; HbA1c = hemoglobin A1c.

Table 4

Comparison of patients that responded more and less drastically to insulin treatment

Characteristics	Group A (more response)	Group B (less response)	*p*
Age (y)	60.6	61.6	0.808
Sex (male:female)	11:14	13:12	0.571
BMI (kg/m^2)	26.5	26.7	0.928
Duration (y)	8.6	10.3	0.366
Baseline fasting glucose (mg/dL)	271.7	182.5	<0.001
Baseline glycated hemoglobin (HbA1c) (%)	10.7	8.6	<0.001
Fasting glucose after 3 m of treatment (mg/dL)	130.7	145.8	0.191
Fasting glucose after 6 mo of treatment (mg/dL)	130.1	153.9	0.081
HbA1c after 3 mo of treatment (%)	7.7	8.2	0.204
HbA1c after 6 mo of treatment (%)	7.1	8.5	0.001

Group A: Patients with HbA1c change ≥1.4% after 6 mo of treatment. Group B: Patients with an HbA1c change of <1.4% after 6 mo of treatment.
BMI = body mass index; HbA1c = hemoglobin A1c.

home, patients can be advised to expect a noticeable drop in blood glucose levels within 6 months of insulin therapy.

The baseline characteristics associated with improved outcomes after 6 months of insulin therapy demonstrated that although both groups had similar baseline HbA1c levels, group 1 exhibited more favorable responses to insulin therapy than group 2. Although the results obtained were not definitive, younger age, male sex, lower BMI, and a shorter history of diabetes were associated with better outcomes after insulin treatment. Additionally, blood glucose levels at 3 months post-treatment initiation did not significantly differ between patients with better and worse responses, suggesting that the 3 months post-treatment blood glucose level does not serve as a good indicator of therapeutic effectiveness.

It is particularly encouraging that the patients in both groups 1 and 2 experienced significant reductions in HbA1c levels after insulin treatment. By the end of 3 months of treatment, HbA1c levels had decreased, on average, by 2.0% in group 1 and 1.3% in group 2. After 6 months of treatment, HbA1c levels were reduced by an average of 2.6% in group 1 and 1.1% in group 2. This highlights the effectiveness of insulin therapy in reducing HbA1c levels.

Patients who achieved greater reductions in HbA1c levels after at least 6 months of treatment had higher baseline fasting blood glucose and HbA1c levels before insulin initiation. In addition to the previously mentioned factors, younger patients, women, those with a lower BMI, or those with a shorter diabetes duration demonstrated a more pronounced response to

insulin therapy. However, the influence of these additional characteristics remains inconclusive in our study and warrants further investigation.

Due to the study design, a significant response was defined by an absolute reduction in HbA1c levels; however, through further analysis of our data, we discovered that group A not only had a greater absolute reduction in HbA1c levels compared to group B (–3.6% vs –0.1%, respectively) but also experienced a greater relative reduction in HbA1c levels (–34% from baseline vs –1% from baseline). Patients in groups A and B showed no significant differences in blood glucose levels at 3 or 6 months post-treatment. Similarly, HbA1c levels did not differ significantly between the groups after 3 months of treatment. However, significant differences in HbA1c levels between the groups became apparent after 6 months of insulin treatment. This suggests that by the end of 6 months of treatment, patients who respond more dramatically to insulin treatment achieve better glycemic outcomes. This finding is particularly promising, especially for patients with initially poor blood glucose control, as it suggests that those with higher baseline levels may achieve substantial and statistically significant reductions in HbA1c levels following insulin therapy.

Patients in both groups experienced significantly reduced HbA1c levels after insulin treatment. After 3 months of treatment, HbA1c levels decreased by an average of 3.0% in group A and 0.4% in group B; after 6 months of treatment, HbA1c levels decreased by an average of 3.6% in group A and 0.1% in group B. These findings underscore the transformative potential of insulin therapy in improving glycemic control in patients with T2DM.

A retrospective analysis with a small sample size cannot fully exclude the possibility of regression to the mean; patients with higher baseline glycemic profiles may naturally trend toward the cohort's mean glycemic profile over time, independent of treatment effectiveness of the treatment. However, the improvement in blood glucose parameters in all patient groups with the initiation of insulin cannot be solely attributed to regression to the mean. Given that the patients in our study had a long-standing history of diabetes before opting for insulin therapy, attributing these effects to regression to the mean would be unwarranted. Other limitations and future points of interest include analyzing the types of oral hypoglycemic agents used before insulin initiation; exploring more comprehensive metabolic profiles of patients who respond differently to insulin therapy, including kidney function, liver function, and lipid panels; and examining differences in dose adjustments among patients with different glycemic responses to insulin treatment. Addressing these limitations is essential for clinical decision-making and necessitates a well-designed study to identify patients who would benefit most from earlier initiation of insulin therapy.

Our study focused on the blood glucose-lowering effects of insulin in patients with diabetes and demonstrated that insulin therapy demonstrated its effectiveness in improving glycemic control. Although we did not assess diabetes-related complications, improved blood glucose control has been shown to reduce microvascular complications in patients with diabetes.[4–6] Currently, the Diabetes Association of the Republic of China recommends an HbA1c target of ≤7% for most patients with diabetes. Overall, 66% of the patients in our study did not achieve an HbA1c of ≤7% 6 months post-treatment. A study conducted in Europe and the United States on patients with T2DM reported similar findings, with 79.1% and 72.2% of those initiating insulin therapy failing to achieve an HbA1c ≤7.0% after 3 and 24 months, respectively.[7] Additionally, the study also associated failure to achieve HbA1c ≤7% during the initial 3 months of therapy with an increased risk of failure to achieve glycemic targets at 2 years of therapy.

Our study results highlight that many patients had been living with diabetes for over a decade, raising important questions about the optimal timing for initiating insulin therapy. Initiating insulin therapy earlier in patients with poorly controlled blood glucose levels should be considered as a strategy to improve glycemic management and reduce complications. Guidelines from the American Diabetes Association recommend initiating basal insulin therapy in patients with T2DM who present with significant hyperglycemia (blood glucose levels ≥300 mg/dL or HbA1c >10%), symptomatic hyperglycemia, or signs of catabolism such as weight loss, hypertriglyceridemia, or ketosis. However, delays in initiating insulin therapy are common. A significant proportion (30%-50%) of patients with diabetes experience prolonged periods of elevated glycemic levels before treatment is initiated.[8,9] Studies have shown that the proportion of patients commencing insulin therapy with an HbA1c ≥9.0% ranged from 23% to 64%,[10] aligning with our study, where 33% of patients started insulin therapy with an HbA1c ≥9.0%. Additionally, another study found that 25% of patients with T2DM experienced an insulin initiation delay of at least 1.8 years, while 50% had a delay of nearly 5 years.[11]

The initiation of insulin therapy in patients with T2DM is highly individualized and often involves extensive discussions between patients and physicians, both of which contribute to delays in initiating therapy.[12] Patients may hold fatalistic beliefs about diabetes progression, lack confidence in insulin's role in management, or have misconceptions regarding the importance of glycemic control. Additionally, physicians may be concerned about hypoglycemia and weight gain or even a lack of confidence in patients to adhere to the prescribed regimen.

Insulin therapy for patients with diabetes will likely play an increasingly vital role in the future. Optimizing the timing, regimen, and communication skills to effectively initiate insulin therapy is of paramount importance for improving outcomes. Recent advances in insulin analogs, such as once-weekly basal insulin, may enhance adherence and mitigate clinical inertia.[13] The implementation of continuous glucose monitoring devices for the care of patients with T2DM may also help clinicians by providing better glycemic control and reducing the incidence of hypoglycemic complications.[14]

In conclusion, significant improvements in HbA1c levels were observed as early as 3 months after the initiation of insulin therapy in patients with poorly controlled T2DM. Patients with higher baseline glycemic profiles exhibited a more pronounced response to insulin treatment. Therefore, timely initiation of insulin therapy should be considered for patients with inadequate diabetes control to achieve better glycemic outcomes.

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