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Predictors of glycemic control after decline of insulin therapy by patients with type 2 diabetes☆

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ABSTRACT

Aim: Decline of insulin therapy by patients is common but poorly investigated. We conducted this study to determine patient and treatment characteristics predictive of glycemic control after declining clinician recommendation to initiate insulin therapy.
Methods: We retrospectively studied adults with type 2 diabetes mellitus treated at two academic medical centers between 1993 and 2014 who declined their healthcare provider recommendation to initiate insulin.
Results: In a multivariable analysis of 300 study patients adjusted for demographics, comorbidities and clustering within providers, higher baseline HbA1c (OR 1.85; 95% CI 1.40 to 2.39; $p < 0.001$) and lifestyle changes (OR 8.39; 95% CI 3.26 to 21.55; $p < 0.001$) were associated with greater, while non-adherence to diabetes medications (OR 0.014; 95% CI 0.0025 to 0.085; $p < 0.001$) and discontinuation of a non-insulin diabetes medication (OR 0.30; 95% CI 0.11 to 0.80; $p = 0.016$) were associated with lower probability of HbA1c decrease after declining insulin therapy.
Conclusion: We identified patient characteristics and treatment strategies associated with success and failure of glycemic control after insulin therapy decline by the patient. This information can assist in selection of optimal therapeutic approaches for these individuals.

1. Introduction

Diabetes is one of the most common chronic diseases, with a worldwide prevalence of 6.4% that is projected to increase to 7.7% by the year 2030.[1,2] The number of people diagnosed with diabetes worldwide has risen from 108 million in 1980 to 422 million in 2014.[3] In the United States, diabetes prevalence is even higher at 12.6%; it is the seventh leading cause of death and contributes to many others.[4,5] In addition to acute complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic non-ketotic state, diabetes can lead to a number of micro- and macrovascular sequelae, including retinopathy, nephropathy, coronary artery disease (CAD) and cerebrovascular accident (CVA).[3,6]

Type 2 diabetes mellitus (T2DM) is characterized by a combination of increased insulin resistance and a decline in beta cell function.[7,8] Patients with T2DM who have elevated blood glucose levels are at high risk for acute and chronic complications[9,10]; lowering blood glucose decreases these risks.[11–13] Consequently, current guidelines recommend that most patients achieve hemoglobin HbA1c levels = 7.0% (53 mmol/mol) or lower.[14–16] As the disease continues to progress, repeated intensification of treatment is usually necessary to achieve these targets.[17]

Multiple medications are available to treat T2DM. However, many of them have limited glucose-lowering effect, common adverse reactions and/or contraindications that restrict their use.[18] Insulin, on the other hand, has no contraindications and high efficacy for lowering blood glucose. As a result, many patients with T2DM require insulin at some point during the course of their disease. Nevertheless, insulin therapy is often delayed.[19] While historically delays in initiation of insulin therapy were thought to be primarily due to clinical inertia,[20,21] recent findings show that many patients with diabetes decline insulin therapy offered to them by their clinicians.[22] The clinical course of patients who have declined insulin therapy remains poorly understood. We have therefore conducted this study aiming to establish the factors associated with a greater risk of poor glycemic control following insulin therapy decline by the patient.

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2. Materials and methods

2.1. Study design

We conducted a retrospective analysis to determine patient characteristics predictive of glycemic control after they declined their healthcare providers' recommendation to start insulin treatment.

2.2. Study cohort

We studied adults with T2DM, treated by primary care physicians or endocrinologists affiliated with Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) who declined an insulin therapy recommendation between January 1, 1993, and December 31, 2014. Patients were considered to have declined insulin therapy recommendation if the provider's EMR note documented both the recommendation of insulin therapy and the patient's rejection of that recommendation in the absence of an insulin prescription. We compared 150 randomly selected patients whose HbA1c subsequently decreased to 150 randomly selected patients whose HbA1c increased or stayed the same after rejecting insulin therapy. Patients were included in the analysis if they were at least 18 years old, declined insulin treatment recommended by their providers for the first time, had no prior history of insulin usage, had HbA1c ≥ 7.0% (53 mmol/mol) at baseline and a follow-up HbA1c measurement at least three months after declining insulin therapy. Patients were excluded if they had a diagnosis of type 1 diabetes or were pregnant. This study was approved by the Partners HealthCare institutional review board, and the requirement for written informed consent was waived.

2.3. Study measurements

Patients' medical history and demographic information were obtained from the Electronic Medical Record (EMR) system at Partners HealthCare, which includes records from BWH and MGH. To identify characteristics predictive of glycemic control, we manually collected demographic information (age, sex, race/ethnicity, primary language, marital status, health insurance and median household income by zip code), baseline measurements (HbA1c, BMI and the number of non-insulin diabetes medications), pre-existing medical conditions (sustained elevated HbA1c, coronary artery disease, cerebrovascular accident, and mental illness) and characteristics of diabetes treatment after declining insulin therapy (lifestyle changes, weight changes, treatment adherence, starting or increasing the doses of a non-insulin diabetes medication, discontinuing or decreasing the doses of a non-insulin diabetes medication, and starting insulin after an initial rejection). Discontinuation or addition of a non-insulin medication was recorded only if the decision was made by the healthcare provider; self-discontinuations of diabetes medications by the patient were recorded as treatment non-adherence. Sustained HbA1c elevation was defined as HbA1c ≥ 7.0% (53 mmol/mol) for at least 12 months prior to having declined insulin with no HbA1c < 7.0% (53 mmol/mol) during this time. Direction of HbA1c change between baseline and the first measurement at least three months after the initial decline of insulin therapy (decreased vs. increased or remained the same) served as a binary primary outcome.

2.4. Statistical analysis

Summary statistics were analyzed using measures of central tendency (means, standard deviations, and medians) for continuous variables and using frequencies and proportions for categorical variables. To identify predictors of HbA1c decrease, we constructed a multivariable logistic regression model that included patient demographics, baseline characteristics and post-insulin decline treatment, and was also adjusted for clustering within individual providers. Multiple imputation was used to account for missing data (BMI and median household income by zip code). Significance threshold was adjusted for multiple hypothesis testing using the Simes-Hochberg method.[23,24] All analyses were performed using SAS, version 9.4 (Cary, NC).

3. Results

We identified 300 patients who rejected insulin treatment recommended by their providers for the first time by randomly selecting 150 patients whose HbA1c decreased after they declined insulin therapy and 150 patients whose HbA1c did not. Baseline characteristics were similar between the two groups (Table 1) with the exception of the baseline HbA1c that was higher for patients whose HbA1c subsequently decreased (9.5% (80 mmol/mol) vs. 8.5% (69 mmol/mol); $p < 0.001$).

Mean follow-up HbA1c was 7.7% (61 mmol/mol) among patients whose HbA1c decreased after they declined insulin therapy recommendation and 9.5% (80 mmol/mol) among the rest. In univariate analysis (Table 1), patients whose HbA1c decreased following decline of insulin therapy were more likely to implement lifestyle changes (27.3% vs. 7.3%; $p < 0.001$) or to initiate a non-insulin diabetes medication (47.3% vs. 31.3%; $p = 0.006$); additionally, individuals who started a non-insulin diabetes medication had, on average, achieved a decrease of 0.4% in HbA1c. Patients whose HbA1c decreased after they declined insulin therapy were also less likely to be non-adherent to diabetes medications (1.3% vs. 26.7%; $p < 0.001$) or to discontinue a non-insulin diabetes medication (8.0% vs. 16.0%; $p = 0.049$) after they declined insulin therapy. There were no statistically significant differences in BMI changes or insulin initiation rate after the initial decline between the two groups.

In a multivariable analysis (Table 2) adjusted for demographics, comorbidities and clustering within providers, we found that higher baseline HbA1c (OR 1.83; 95% CI 1.40 to 2.39; $p < 0.001$) and lifestyle changes implemented after the initial decline of insulin therapy (OR

Table 1
Characteristics of study patients.

	HbA1c decreased n = 150	HbA1c did not decrease n = 150	p-Value
Baseline			
Age, mean (SD), y	62 (14.1)	62.5 (13.2)	0.72
Female sex, no (%)	79 (52.6)	81 (54)	0.90
White race, no (%)	99 (66)	97 (64.6)	0.90
English as primary language, no (%)	120 (80)	119 (79.3)	1
Married, no (%)	70 (46.6)	72 (48)	0.90
Government insurance, no (%)	86 (57.3)	83 (55.3)	0.81
Median household income, mean (SD), $1000s	62.6 (23.5)	66.8 (26.0)	0.14
HbA1c, mean (SD), %/mmol/mol	9.5/80 (1.9)	8.5/69 (1.3)	<0.001
BMI, mean (SD), kg/m^2	32.9 (5.9)	33.1 (6.5)	0.78
Non-insulin diabetes medications, mean (SD)	1.7 (0.74)	1.8 (0.75)	0.19
Sustained elevated HbA1c, no (%)	99 (66)	108 (72)	0.31
CAD, no (%)	24 (16)	27 (18)	0.75
CVA, no (%)	9 (6)	5 (3.3)	0.41
Mental illness, no (%)	24 (16)	31 (20.6)	0.37
Study year, mean (SD)	13.4 (3.7)	13.1 (4.2)	0.43
Post insulin decline			
HbA1c, mean (SD), %/mmol/mol	7.7/61 (1.3)	9.5/80 (1.8)	<0.001
Lifestyle changes, no (%)	41 (27.3)	11 (7.3)	<0.001
Weight loss >5%, no (%)	7 (4.6)	12 (8)	0.34
Weight loss <5%, no (%)	57 (38)	47 (31.3)	0.27
Weight gain, no (%)	44 (29.3)	46 (30.6)	0.89
Non-adherence, no (%)	2 (1.3)	40 (26.7)	<0.001
Non-insulin diabetes medication started or increased, no (%)	71 (47.3)	47 (31.3)	0.006
Non-insulin diabetes medication discontinued or decreased, no (%)	12 (8)	24 (16)	0.049
Insulin started, no (%)	15 (10)	18 (12)	0.71
No changes, no (%)	16 (10.6)	25 (16.6)	0.17

Table 2
Effects of patient and treatment characteristics on glycemic control.

	Odds ratio	95% CI	p-Value
Baseline			
Age	1	0.97–1.03	0.60
Female sex	1.39	0.75–2.57	0.29
White race	1.26	0.58–2.71	0.55
English as primary language	1.25	0.52–3.03	0.61
Married	0.84	0.46–1.52	0.57
Government insurance	1.31	0.65–2.66	0.43
Median household income	0.98	0.97–1.00	0.06
HbA1c	1.83	1.40–2.39	**<0.001**
BMI	0.99	0.94–1.05	0.95
Non-insulin diabetes medications	1.2	0.77–1.86	0.41
Sustained HbA1c elevation	0.65	0.34–1.25	0.20
CAD	0.66	0.33–1.32	0.24
CVA	1.18	0.28–4.96	0.81
Mental illness	0.67	0.30–1.45	0.31
Study year	1.06	0.97–1.15	0.15
Post insulin decline			
Lifestyle changes	8.39	3.26–21.55	**<0.001**
Weight loss >5%	1.05	0.27–3.96	0.93
Weight loss <5%	0.92	0.31–2.69	0.88
Weight gain	0.53	0.17–1.60	0.26
Non-adherence	0.014	0.002–0.08	**<0.001**
Non-insulin diabetes medication started or increased	1.73	0.84–3.59	0.13
Non-insulin diabetes medication discontinued or decreased	0.3	0.11–0.80	**0.016**
Insulin started	1.26	0.49–3.26	0.62
No changes	0.48	0.12–1.85	0.29

Boldfaced p-values were significant after Simes-Hochberg adjustment for multiple hypothesis testing.

8.39; 95% CI 3.26 to 21.55; $p < 0.001$) were associated with greater probability of HbA1c decrease, while non-adherence to diabetes medications (OR 0.014; 95% CI 0.0025 to 0.085; $p < .001$) and discontinuation of a non-insulin diabetes medication (OR 0.30; 95% CI 0.11 to 0.80; $p = 0.016$) were associated with lower probability of HbA1c decrease after initial decline of insulin therapy by the patient. After the Simes-Hochberg procedure with a false discovery rate of 25% the same variables remained statistically significant.

The most common reasons for discontinuation of a non-insulin diabetes medications after the initial decline of insulin therapy recommendation by the patient (Table 3) were replacement with insulin (presumably due to lack of efficacy), side effects or worsening renal function.

4. Discussion

In this study, we found that characteristics of patients who had declined their healthcare providers' recommendation to start insulin therapy could indicate their subsequent glycemic control. Individuals with higher baseline HbA1c were more likely to achieve a decrease in their blood glucose levels. This could be explained by greater motivation of the patients who recognize they are at higher risk of complications of diabetes and may also be symptomatic from their hyperglycemia, as well as their physicians who may be treating them more aggressively[25,26] On the other hand, a "regression to the mean" could also be a contributing factor. Higher baseline HbA1c could have been a transient event, caused by a temporary lapse in diet or medication, that improved after their restoration.

Treatment of these patients after they had declined insulin therapy was also an important factor in their subsequent glycemic control. Our results were consistent with previously published studies that suggest that the initiation of a new class of non-insulin diabetes medication added to the initial therapy generally lowers HbA1c around 0.4 to 1.0%.[27] Intensification of alternative anti-hyperglycemic therapy is a reasonable step in patients who may benefit from treatment with insulin but decline it; even if a single non-insulin diabetes medication fails to achieve glycemic goals, multiple agents together may be successful.[14] Furthermore, a number of recently introduced diabetes agents, including GLP-1 receptor agonists and SGLT2 inhibitors have additional short-and long-term clinical benefits besides lowering blood glucose and may for some patients be preferable to treatment with insulin.[14,28,29]

Another aspect of post-insulin therapy decline treatment that was strongly associated with improving glycemic control was the implementation of lifestyle changes. Current guidelines recommend lifestyle management as a fundamental aspect of diabetes care, including diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care.[14] Effect of lifestyle counseling on blood glucose levels is supported by both clinical trials[30,31] and real-world evidence.[32,33] Our evidence suggests lifestyle changes could improve glycemic control even after a significant progression of the disease and have an impact on the patient clinical outcome. However, given the retrospective nature of the analysis and the observed dramatic effect of lifestyle counseling, it is possible that a reporting bias was also a contributing factor.

We also identified several factors that were associated with worsening glycemic control after the decline of insulin therapy recommendation. One of these was the discontinuation of non-insulin diabetes medications. In both groups, these were most commonly stopped because they were being replaced with insulin (likely due to lack of efficacy) or side effects. On the other hand, a numerically larger proportion of patients whose HbA1c did not decrease following decline of insulin therapy discontinued non-insulin medications due to worsening of their renal function, which could have contributed to the poor glycemic control of this group. Consequently, the causal relationship between discontinuation of non-insulin diabetes medications and glycemic deterioration could have been bi-directional. Another important factor that was associated with a lack of improvement in glycemic control was non-adherence to diabetes medications. While reporting bias could have accounted for some of the magnitude of the observed effect, non-adherence to diabetes therapy is well established as a significant contributor to suboptimal glycemic control and is an important risk factor for chronic complications and high mortality rates among patients with T2DM.[34–36]

We also found that some of the post-insulin decline treatment characteristics were not associated with changes in blood glucose level, as might have been expected. Weight loss, whether under or in excess of 5% of body mass, did not show a statistically significant association with HbA1c changes. This could have been due to the time it takes both to lose the weight – not an instantaneous process – and for the HbA1c to achieve equilibrium. As the outcome HbA1c could have been measured as early as three months after the patient's entry into the study (decline of insulin therapy), there may not have been sufficient time for the weight loss to manifest itself in HbA1c changes. On the other hand, catabolic weight loss due to insulin deficiency is a less likely explanation, as all patients in our study had type 2 diabetes.

Table 3
Reasons for discontinuation of non-insulin diabetes medications during follow-up.

	HbA1c decreased n = 12	HbA1c did not decrease n = 24	p-Value[a]
Initiation of insulin, no (%)	4 (33.3)	9 (37.5)	1.0
Deterioration of kidney function, no (%)	1 (8.3)	3 (12.5)	1.0
Side effects, no (%)	3 (25.0)	6 (25.0)	1.0
Initiation of chemotherapy, no (%)	1 (8.3)	0	0.33
Not specified, no (%)	3 (25.0)	6 (25.0)	1.0

[a] p-Values were calculated using Fisher's exact test.

Initiation of insulin therapy after the patient originally declined it also was not associated with improvement in blood glucose control. While this contrasts from published evidence that suggests that the addition of basal insulin to any non-insulin combination is a highly effective approach,[37] it is worth noting that our study included patients who were originally disinclined to take insulin. It would therefore not be unexpected if these individuals did not actually start insulin therapy when it was ultimately prescribed by their clinicians, or were only partially adherent to it. Even in general population of patients with T2DM non-adherence to diabetes medications reaches as high as 60% and many patients do not adhere to either oral or injectable treatment after the first six months of therapy.[34] It would therefore not be surpring if in our study population of individuals reluctant to initiate insulin therapy this number would be even higher. Non-adherence to insulin, in particular, could also be explained by its continuously rising costs, which create a substantial economic burden on patients with diabetes.[38]

A number of previous studies on decline of insulin therapy aimed to define the concept and causes of psychological insulin resistance from the perspective of patients with T2DM. This phenomenon can result from a variety of beliefs that include cognitive appraisal, emotional reactions, and supportive relational factors.[39,40] These studies have pointed out the need for adequate psychological insulin resistance measurement tools such as questionnaires,[41] and proper patient training to decrease decline of insulin therapy.[40] However, many of them did not include patients who actually declined insulin therapy (most asked patients who have not been treated with insulin to comment on a hypothetical scenario of insulin therapy recommendation). Furthermore, none of them studied patient outcomes after decline of insulin therapy.

As we are starting to gather systematic information about decline of insulin therapy by patients, it may seem intuitive that such decisions would inexorably lead to poor clinical outcomes. However, many patients who reject insulin therapy subsequently see an improvement of their glycemic control. The present study, for the first time, identifies patient and treatment characteristics that are associated with either increase or decrease in blood glucose levels following decline of insulin therapy by the patient. While some of these may in retrospect seem obvious (e.g. association of lifestyle changes with lower and non-adherence with higher blood glucose levels), others were less apparent (e.g. lack of association between eventual initiation of insulin and glycemic control). This study will therefore serve as one of the initial building blocks for an evidence-based approach to treatment of patients with type 2 diabetes who decline insulin therapy.

Our study had a number of strengths. It included a racially and socioeconomically diverse population receiving attention in primary care settings where most patients with diabetes in the United States are treated. The availability of comprehensive electronic medical record data over an extended period offered a unique viewpoint into a previously unexplored but apparently common phenomenon of the decline of insulin therapy by patients.

The present study leveraged these strengths to add to the existing literature a novel perspective on decline of insulin therapy by patients – analysis of its outcomes. For the first time, we were able to identify baseline patient characteristics and subsequent therapeutic actions that are associated with improved glycemic control after decline of insulin therapy recommendation by the patient. These findings could help guide clinicians to optimize a patient-centered approach to individuals who declined insulin therapy. Even when insulin therapy is the best recommended course of action, other alternative approaches may exist that will help the patient achieve blood glucose control; the findings of this study offer initial data on strategies that are more likely to be successful under these circumstances.

4.1. Limitations

The findings of this study should be interpreted in light of its limitations. As an observational analysis, it could only identify associations rather than causal relationships. Therefore the findings of the study may not be rigorous enough to definitively justify modifications of existing clinical practice. The study may not have been powered to detect the relationship between glycemic control and some of the variables, such as the initiation of non-insulin diabetes medications. While we incorporated multiple potential confounders in the multivariable analysis and also adjusted for clustering within individual providers, it is possible that some confounders were not included. Not matching the two study groups on baseline HbA1c levels may have introduced a bias because the same diabetes medications (added after the initial decline of insulin therapy by the patient) would have a greater glucose-lowering effect in patients with higher HbA1c. Potentially relevant information, such as the intensity of lifestyle changes or the magnitude of medication non-adherence, was not available for most study patients. Reporting bias could have affected some aspects of the analysis; for example, the relationship between HbA1c changes and lifestyle changes or medication non-adherence. Finally, this study was conducted in academically affiliated practices in eastern Massachusetts. Therefore, our findings may not be applicable to other settings.

4.2. Future directions

In view of the limitations discussed above, the initial findings provided by the present study need to be confirmed by subsequent research to provide more definitive guidance to clinicians and patients. These future investigations could take form of larger observational studies, patient and provider surveys or – ideally – interventional trials that could test the efficacy of different treatment methods after decline of insulin therapy recommendation by the patient on their glycemic control. Data presented in this study could help formulate the questions to be addressed by subsequent investigations and assist in their design.

5. Conclusion

Our results suggest that after declining of insulin therapy by patients, specific patient characteristics (e.g. baseline glucose levels) and therapeutic actions (e.g. lifestyle changes and treatment adherence) could lead to better glycemic control. These findings could help guide clinicians to optimize a patient-centered approach to individuals who declined insulin therapy in order to achieve glycemic targets. Further prospective interventional investigations are needed to establish the optimal treatment strategies and outline a provider-patient discussion approach that ensures that individuals make fully informed choices while optimizing clinical outcomes.

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