Impact of Adherence and Weight Loss on Glycemic Control in Patients with Type 2 Diabetes: Cohort Analyses of Integrated Medical Record, Pharmacy Claims, and Patient-Reported Data

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ABSTRACT

BACKGROUND: Managed care organizations put great effort into managing the population of patients with type 2 diabetes mellitus (T2DM) because of the health and economic burden of this disease. In patients with T2DM, weight loss and glycemic control are primary treatment aims to help improve patient outcomes, but these goals are not easily achieved. While achieving these aims requires a multifaceted approach of drug therapy management and lifestyle modification, truly understanding the role of medication adherence in achieving these outcomes is important for both patient and population management. This study expands on existing evidence that weight loss is associated with improved glycemic control by examining the role of medication adherence in achieving these goals in a managed care setting. This study is unique in that these associations are evaluated using multiple sources of data, including medical records for treatment outcomes, pharmacy claims, and patient-reported data to assess medication adherence. These data sources represent those typically available to payers or providers.

OBJECTIVE: To describe the relationships between medication and adherence, weight change, and glycemic control in patients with T2DM.

METHODS: This historical cohort study included adult patients with T2DM in a large integrated health system and was based on electronic health record and pharmacy claims data from November 1, 2010, through October 31, 2011, as well as data from a self-reported adherence survey conducted in March 2012. Included patients received a diabetes medication from a therapeutic class not previously received, between November 1, 2010, and April 30, 2011 (index date), who had blood glucose (HbA1c) and weight values at index date and 6 months follow-up, participated in an adherence survey, and had ≥1 prescription claim for the index-date drug. Associations between the dual outcomes of weight loss (≥3%) and HbA1c control (<7.0%), while controlling for medication adherence and other demographic, treatment, and clinical variables, were evaluated using structural equation models (SEM). Separate models adjusted for different measures of medication adherence—self-reported using the 5-item Medication Adherence Rating Scale (MARS-5) and a modified medication possession ratio (mMPR) from pharmacy claims data.

RESULTS: The study included 166 patients with a mean age of 61.1 (standard deviation = 12.1) years; 56.0% were female. Medication adherence was high, with 72.2% adherent using MARS-5 and 77.1% using mMPR measures. The SEMs found that only self-reported medication adherence is associated with weight loss (MARS-5: OR = 1.70, 95% CI = 1.11-2.60), while both self-reported and claims-based medication adherence were associated with HbA1c < 7.0% (MARS-5: OR = 1.59, 95% CI = 1.09-2.34; mMPR: OR 2.71, 95% CI = 1.22-5.98). Further, weight loss is significantly associated with HbA1c < 7.0% (MARS-5: OR = 3.60, 95% CI = 2.39-5.46; mMPR: OR 2.99, 95% CI = 1.45-6.17).

CONCLUSIONS: This study has provided additional evidence in a managed, integrated setting that in patients treated for T2DM, weight loss is associated with good glycemic control. Adherence is associated with weight loss according to self-report, but not claims-based adherence measures. Adherence is also associated with glycemic control as measured by the 2 different methods. This study adds to the body of literature highlighting the importance of adherence as well as weight loss in achieving good glycemic control. The fact that the association of weight loss and adherence on glycemic control outcomes was significant regardless of medication adherence method is important in payer-provider collaborations, where access to data sources to evaluate adherence may vary. This study also supports continued investment in weight loss and adherence programs in the management of patients with T2DM.

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What is already known about this subject

- Good glycemic control helps reduce the risk of diabetes-related complications in patients with type 2 diabetes.
- Weight loss is associated with improved glycemic control in patients with type 2 diabetes.
- Medication adherence is associated with improved glycemic control in diabetes.

What this study adds

- The study shows the specific relationship of adherence with weight loss and glycemic control (i.e., adherence influences weight loss as measured by self-report, and adherence influences glycemic control as measured by either self-report or claims-based methods).
- Structural equation models are valuable tools to demonstrate the association between contributing variables in diabetes outcomes.

Diabetes affects an estimated 26 million people in the United States with approximately $176 million per year in direct medical costs.[1] A vast majority of patients with diabetes have type 2 diabetes mellitus (T2DM), a population that is typically also overweight or obese.[2,3] Unfortunately, both T2DM and obesity are independently associated with poor cardiovascular outcomes.[4,5] However, weight loss as little as 1 kilogram has been associated with improvements in

glycemic control, blood pressure, and lipid outcomes in patients with T2DM.[6-9] As a result, weight management has become increasingly important in patients with T2DM.[10-12]

Because of the high costs of care and risk of complications that negatively impact quality of life, T2DM is often a top priority for population management within managed care organizations and for providers. However, achieving treatment goals of weight loss and glycemic control can be difficult. Attaining these goals requires multifaceted interventions, involving significant lifestyle modifications that include diet and exercise changes. An additional challenge for patients with T2DM trying to manage their weight is that several diabetes medications are associated with weight gain.[13] Conversely, several other antidiabetic medications are associated with weight loss or weight neutrality, and these agents can be used as treatment alternatives in patients with concurrent weight loss goals.[14-17]

Adherence to diabetes medications is another important aspect of managing patients with T2DM and has been associated with improved glycemic control.[18-20] Medication adherence is complex, involving multiple patient behavioral components, including medication acquisition and prescription filling, comprehending the instructions from the prescriber and following them, and remembering to take the medication. Various methods are available to assess adherence, but they measure different behavioral components of adherence. For instance, adherence measures that are based on pharmacy claims data, available to payers and to some providers via integrated electronic health records, can be used to examine the duration and extent of medication possession and are used as a surrogate for actual drug taking.[21] Self-reported adherence measures attempt to examine whether or not patients are taking the medication as prescribed but may be subject to reporting bias.[22] Self-reported measures of adherence can be used to examine intentional and unintentional adherence behaviors.[23] A concern for payers and providers collaborating on the care of populations is that these different components of adherence may not be correlated; therefore, it is questionable whether these different measures can be used interchangeably to predict outcomes. These concerns are appropriate, as the agreement between self-reported and claims- or refill-based measures of adherence is mixed, with most studies reporting a weak correlation.[24-35] Yet, whether these measures are similar in impacting outcomes is unknown and is an issue that should be of concern to payer and provider collaborative efforts to manage a population of patients with diabetes.

The purpose of this study was to examine the relationships between medication adherence and weight change on glycemic control in patients with T2DM prescribed a class of diabetes medication not previously used. Self-reported and claims-based measures of adherence were used to examine whether the association between adherence, weight change, and glycemic control were altered when different types of adherence measures were used.

Methods

Patients and Data

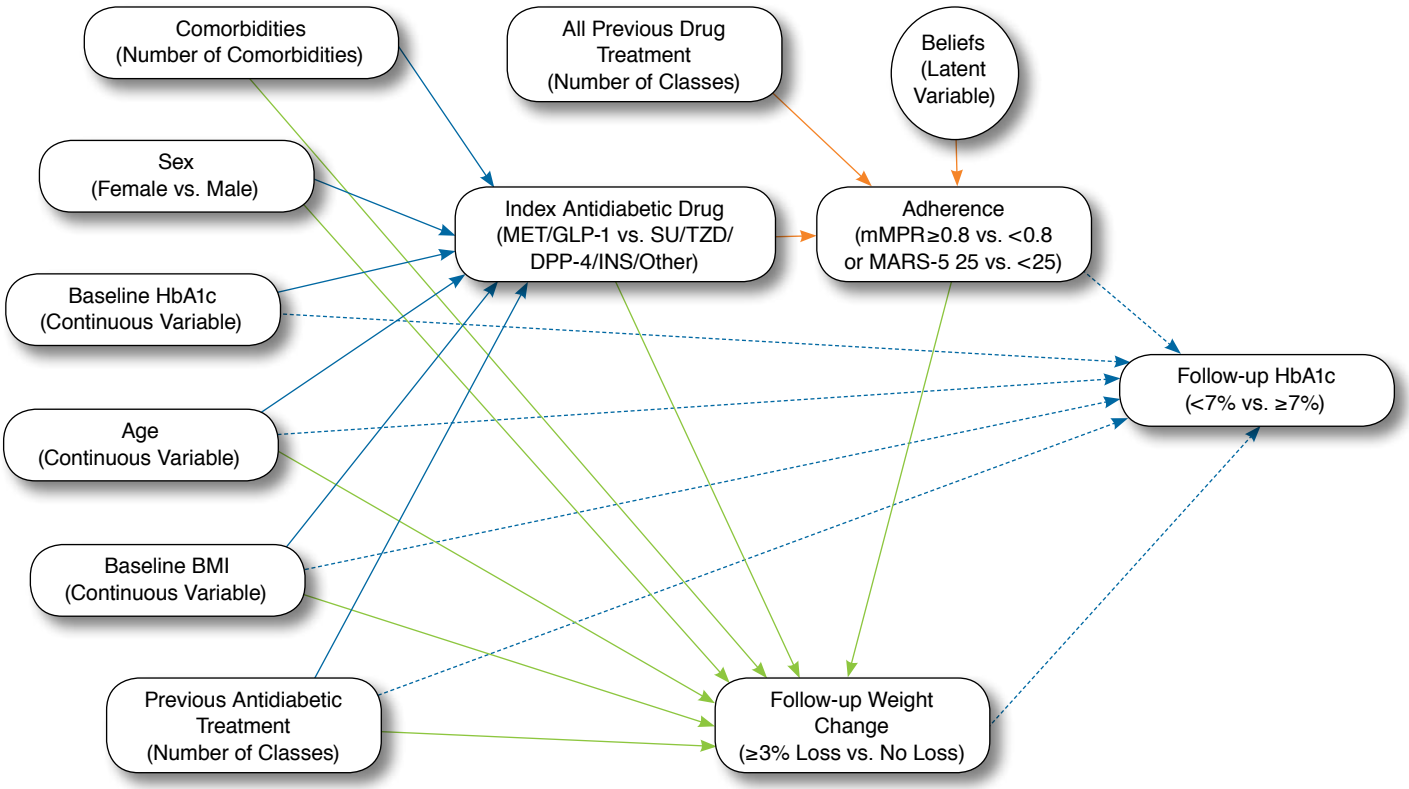
This was a historical cohort study of patients treated in the Geisinger Health System (GHS) from January 1, 2009, to October 31, 2011. GHS is an integrated health system in central Pennsylvania that serves more than 3 million patients and comprises more than 880 physicians. Additionally, GHS is affiliated with Geisinger Health Plan (GHP), one of the largest rural health maintenance organizations in the United States. Nearly one-third of GHS patients have insurance coverage through GHP. Data for this study were acquired from 3 sources, the GHS electronic medical record (EMR), GHP pharmacy claims, and a survey of GHS patients with T2DM.

Patients were included in the study if they had T2DM and were prescribed a class of diabetes medication not previously prescribed between November 1, 2010, and April 30, 2011. Patients were identified as having T2DM by *International Statistical Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code (250.x0 or 250.x2), fasting blood glucose ≥ 126 milligram per deciliter (mg/dL), random blood glucose ≥ 200 mg/dL, hemoglobin A1c (HbA1c) ≥ 7.0%, or a prescription order for an oral diabetes medication. The index date was defined as the date of the new diabetes medication class prescription order. Diabetes drug classes included metformin (MET), sulfonylureas (SU), thiazolidinediones (TZD), dipeptidylpeptidase-4 inhibitors (DPP-4), glucagon-like peptide-1 agonists (GLP-1), insulin (INS), or others (e.g., meglitinides, pramlintide, or α-glucosidase inhibitors). Patients included in this study were required to have measurements of HbA1c and weight at index date (-90/+30 days) and at 6 months post-index date (± 90 days) in the EMR, with ≥ 90 days between the baseline and follow-up HbA1c measures. Patients were excluded if they had type 1 diabetes (ICD-9-CM 250.x1 or 250.x3), if they were prescribed ≥ 2 new diabetes medication classes on the index date, including fixed-dose combinations; if they had a diagnosis for dementia or other cognitive impairment that may have affected their ability to answer survey questions; or if they resided in a nursing home. Finally, patients were required to have GHP coverage, at least 1 prescription claim for the index drug, and a GHS physician as their primary care provider.

Self-Reported Adherence

Of the patients identified in the EMR, 1,000 were randomly selected, regardless of GHP coverage, and invited to participate in a telephone survey that included a validated adherence questionnaire and additional adherence-related questions developed by the authors of this study. The survey was conducted in March 2012, approximately 9 to 15 months after the index date. Patients were contacted by trained interviewers, and up to 15 attempts were made to reach each patient. Patients were

FIGURE 1 Structural Equation Model (SEM)[a]



[a]*SEM associations examined in the current study, allowing simultaneous examination of multiple endogenous and exogenous variables. In this diagram, endogenous variables are predicted by other variables and exogenous variables are not.*

BMI = body mass index; DPP-4 = dipeptidylpeptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; INS = insulin; MARS-5 = 5-item Medication Adherence Rating Scale; MET = metformin; mMPR = modified medication possession ratio; Other = meglitinides, pramlintide, or α-glucosidase inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

asked to report adherence to the index drug during the first month of treatment using the validated, 5-item Medication Adherence Rating Scale (MARS-5).[36,37] A score of 25 was considered adherent, while a score of <25 was considered nonadherent. Through 15 additional questions developed by the authors, patients were also asked to report their reasons for nonadherence, their perceptions about treatment-related weight gain or loss, health care professional communication of treatment-related weight effects, and weight changes they experienced, if any, during treatment with the index diabetes medication.

Claims-Based Adherence

GHP pharmacy claims data were used to calculate claims-based adherence. Adherence was calculated using the modified medication possession ratio (mMPR), which calculates adherence as the total days supplied divided by the number of days from the first claim to the last claim plus the days supplied on the last claim.[21] The mMPR was selected because it most closely reflects the time frame and manner that patients were asked via the survey to report adherence. A calculated mMPR ≥0.8 was considered adherent, whereas <0.8 was considered nonadherent.

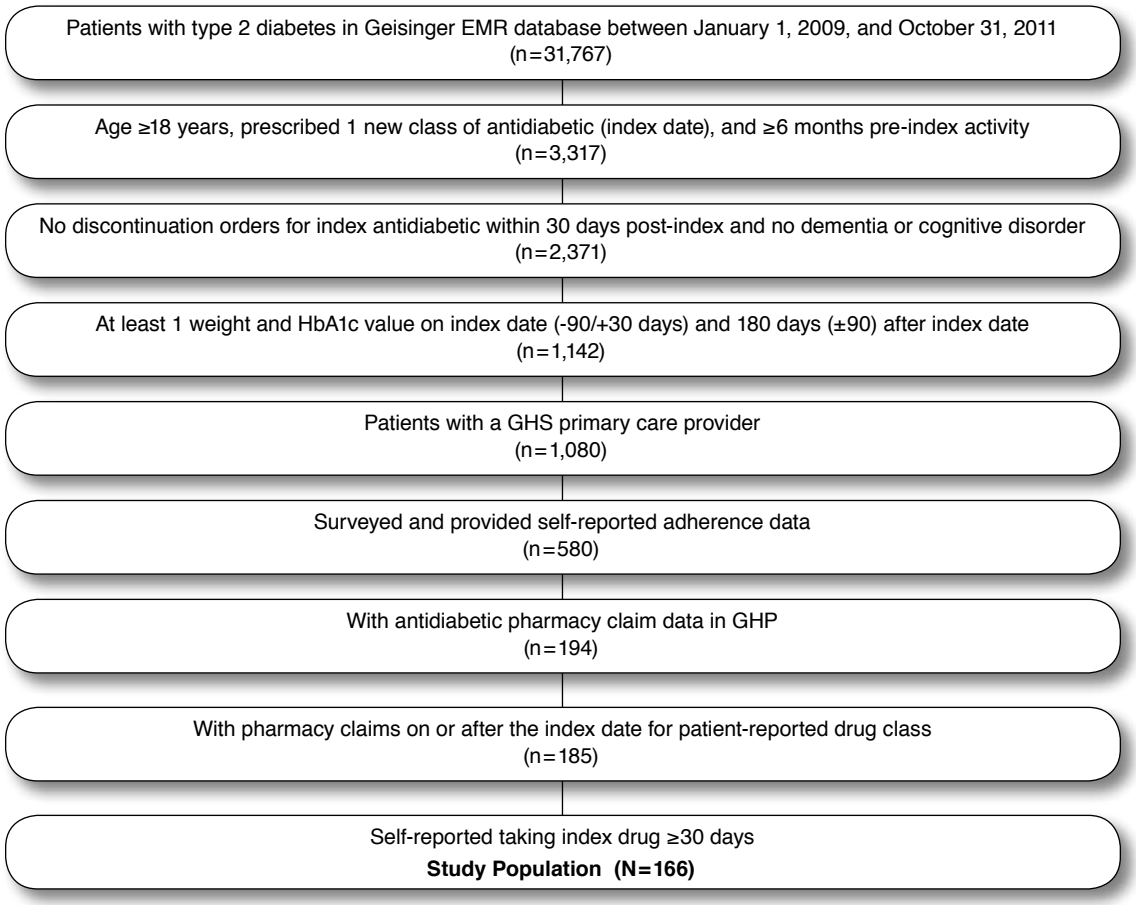
Outcomes

Glycemic control and weight outcomes were derived from the EMR at 6 months post-index date (±90 days). Outcomes were dichotomized, with glycemic control defined as an HbA1c <7.0% (vs. ≥7.0%) and weight loss defined as a ≥3% decrease in body weight (vs. no weight loss or weight loss <3%). A change in body weight of at least 3% was used because it is not likely due to measurement error or normal weight fluctuations and is also considered clinically meaningful.[38,39]

Statistical Analyses

Descriptive statistics were used to report the baseline characteristics of the study cohort overall and stratified by index-date diabetes drug class, grouped by drugs with weight loss properties (MET,[16,17] GLP-1) or drugs with weight neutral or

FIGURE 2 Patient Identification Flowchart



EMR = electronic medical record; GHS = Geisinger Health System; GHP = Geisinger Health Plan; HbA1c = hemoglobin A1c.

weight gain properties (SU, TZD, DPP-4, INS, others). To assess the effect of the index drug on weight despite prior therapy, patients were assigned to the drug group based only on the index diabetes drug. Baseline characteristics were compared between drug groups using independent t-tests for continuous variables and chi-square or Fisher's exact tests as appropriate for categorical variables. The proportion of patients classified as adherent was compared between drug groups using chi-square tests. Paired t-tests were used to examine weight and HbA1c changes from baseline to 6 months (±90 days) in the adherent and nonadherent groups. Additionally, independent t-tests were used to examine unadjusted differences in weight and HbA1c changes between adherent and nonadherent patients.

Structural equation models (SEM) were developed to simultaneously assess the associations between diabetes medication adherence, weight change, and attaining HbA1c goal while controlling for drug group and baseline characteristics (Figure 1). SEMs were needed for the analysis because they allow for multiple endogenous and exogenous variables, as well as latent variables.[40] Exogenous variables are similar to predictor variables in linear or logistic regression because they are used as predictors and are not themselves predicted by other variables. Baseline characteristics were included as exogenous variables in this study (age, sex, comorbidities, baseline HbA1c, baseline body mass index, previous diabetes medication treatment, and all previous treatments). Endogenous variables are similar to outcome variables in linear or logistic regression because they are predicted by other variables. However, they are dissimilar in that there may be more than 1 endogenous variable, and they may also be used to predict other endogenous variables. In this study, endogenous variables included index date drug group, adherence, weight change, and HbA1c change. Latent variables are variables that are not directly measured in data but are derived from other observed or measured variables. In this study, patient medication beliefs and experiences were assessed as a latent variable derived from corresponding ques-

TABLE 1 Baseline Characteristics of Study Population Stratified by Index Drug Group[a]

	Overall (N = 166)		Weight Loss (MET/GLP-1) (n = 58)		Weight Gain/Neutral (SU/TZD/DPP-4/INS/Other) (n = 108)		
	n	%	n	%	n	%	*P* Value
Demographics							
Age							
Mean (SD)	61.1	12.1	59.0	12.8	62.2	11.6	0.104
< 65	98	59.0	38	65.5	60	55.6	0.213
≥ 65	68	41.0	20	34.5	48	44.4	
Sex							
Male	73	44.0	28	48.3	45	41.7	0.413
Female	93	56.0	30	51.7	63	58.3	
Race							
Caucasian	164	98.8	57	98.3	107	99.1	0.999
African-American	2	1.2	1	1.7	1	0.9	
Clinical characteristics							
Baseline weight (kg), mean (SD)	98.8	22.5	102.4	22	96.8	22.6	0.126
Baseline BMI (kg/m^2), mean (SD)	35.3	7.9	36.2	7.7	34.8	8.1	0.281
Baseline HbA1c (%)							
Mean (SD)	8.1	1.6	8.2	1.7	8.1	1.5	0.697
Median (range)	7.7	5.4-13.9	7.7	5.9-13.4	7.7	5.5-13.9	
Comorbidities							
Coronary heart disease	46	27.7	17	29.3	29	26.9	0.736
Chronic kidney disease	64	38.6	14	24.1	50	46.3	0.005
Hypertension	133	80.1	45	77.6	88	81.5	0.549
Dyslipidemia	155	93.4	54	93.1	101	93.5	0.999
Cerebrovascular disease	14	8.4	5	8.6	9	8.3	0.949
Stroke	2	1.2	1	1.7	1	0.9	0.999
Myocardial infarction	4	2.4	1	1.7	3	2.8	0.999
Microvascular complications	24	14.5	4	6.9	20	18.5	0.062
Thyroid disease	34	20.5	11	19.0	23	21.3	0.723
Depression	32	19.3	9	15.5	23	21.3	0.368
Nonalcoholic fatty liver disease	8	4.8	2	3.4	6	5.6	0.715
Number of prior diabetes drug classes used							
0	51	30.7	42	72.4	9	8.3	< 0.001
1	40	24.1	4	6.9	36	33.3	
2	35	21.1	7	12.1	28	25.9	
3	28	16.9	4	6.9	24	22.2	
≥ 4	12	7.2	1	1.7	11	10.2	

[a]*All figures other than P values are given as n (%), except for cells in green, as labeled in the left-hand column.*

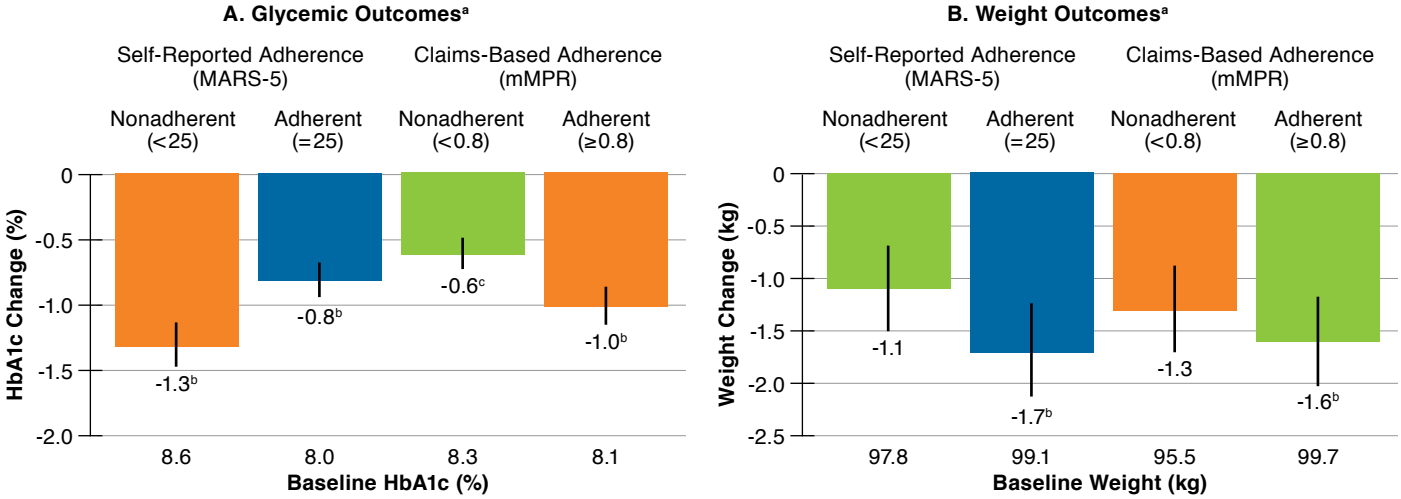
BMI = body mass index; DPP-4 = dipeptidylpeptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; HbA1c = hemoglobin A1c; INS = insulin; kg/m^2 = kilogram per square meter; MET = metformin; Other = meglitinides, pramlintide, or α-glucosidase inhibitors; SD = standard deviation; SU = sulfonylureas; TZD = thiazolidinediones.

tions on the survey (i.e., perceptions about treatment-related weight changes, weight changes experienced, and communication from a health care provider about treatment-related weight changes). Figure 1 details the relationships between variables explored in the SEMs in this study. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC), and the SEM analyses were performed using Mplus 6.11 (Muthen & Muthen, Los Angeles, CA). The study was reviewed and approved by the institutional review boards at the University of Utah and Geisinger Health Systems.

Results

The GHS EMR had 31,767 patients with T2DM during the study period. Of those, 580 patients responded to the survey and provided information on adherence, and only 166 patients met all the inclusion criteria, including having GHP coverage and at least 1 pharmacy claim for the patient-reported index date medication (Figure 2). Baseline characteristics of patients by the 2 treatment groups are reported in Table 1. The mean age (with standard deviation [SD]) of the overall cohort was 61.1 (SD = 12.1) years, and the majority of patients were female

FIGURE 3 Glycemic and Weight Outcomes for Adherent and Nonadherent Patients



[a]*Error bars indicate standard error.*
[b]*Change from baseline P<0.001.*
[c]*Change from baseline P<0.05.*
HbA1c = hemoglobin A1c; kg = kilogram; MARS-5 = 5-item Medication Adherence Rating Scale; mMPR = modified medication possession ratio.

(56.0%). Mean baseline HbA1c was 8.1% (SD = 1.6), but there was no difference in HbA1c between the drug treatment comparison groups. The weight loss drug group had a significantly higher proportion of treatment-naïve patients compared with the weight gain/neutral group (72.4% vs. 8.3%, $P<0.001$). These patterns likely reflect the recommendations for the use of MET as first-line therapy, except when patients have reduced renal function or other contraindications.

Overall, diabetes medication adherence in the study was high, with 72.3% classified as adherent based on self-reported data and 77.1% from claims data. However, the agreement between the scales was low (kappa coefficient = 0.142), with 58.4% classified as adherent on both scales, and 9.0% of patients classified as nonadherent on both scales. The proportion of patients determined to be adherent did not differ significantly between drug groups for either adherence measure.

In the unadjusted analyses, patients had statistically significant reductions in HbA1c from baseline to follow-up overall ($P<0.001$) and when stratified by adherence (Figure 3). However, there was not a statistically significant difference in HbA1c change between the adherent and nonadherent groups for either measure of adherence (MARS-5: $P=0.100$; mMPR: $P=0.163$). Adherent patients, using both the self-report and claims-based measures, had significant changes in body weight from baseline ($P<0.001$ for both), but nonadherent patients did not. However, similar to HbA1c change, there was no significant difference in changes from baseline between the adherent and nonadherent patients (MARS-5: $P=0.446$; mMPR: $P=0.771$).

When using the SEMs to control for potential confounders, the results based on either self-reported (MARS-5) or claims-based (mMPR) adherence were similar (Table 2). The only exogenous variable significantly associated with selection of drug treatment was the number of diabetes medication classes previously prescribed. The greater the number of classes previously prescribed, the lower the odds of being prescribed a diabetic medication associated with weight loss (MARS-5: odds ratio [OR] = 0.25, 95% confidence interval [CI] = 0.18-0.35; mMPR: OR = 0.32, 95% CI = 0.19-0.55). None of the considered variables were significantly associated with adherence in either model.

In both models, the weight loss diabetes medication group was associated with weight loss ≥3% (MARS-5: OR = 2.96, 95% CI = 1.93-4.60; mMPR: OR = 3.53, 95% CI = 1.60-7.80) relative to the weight gain/neutral diabetes medication group. However, only the SEM using MARS-5 self-reported adherence found that adherence was significantly associated with weight loss (MARS-5: OR = 1.70, 95% CI = 1.11-2.61; mMPR: OR = 1.59, 95% CI = 0.66-3.83).

In both SEMs, weight loss ≥3% (MARS-5: OR = 3.60, 95% CI = 2.39-5.46; mMPR: OR = 2.99, 95% CI = 1.45-6.17) and adherence (MARS-5: OR = 1.59, 95% CI = 1.09-2.34; mMPR: OR = 2.70, 95% CI = 1.22-5.98) were associated with being at HbA1c goal at 6 months. In contrast, higher baseline HbA1c was associated with a lower likelihood of being at HbA1c goal (MARS-5: OR = 0.71, 95% CI = 0.62-0.82; mMPR: OR = 0.70, 95% CI = 0.53-0.92).

TABLE 2 Results of the Structural Equation Models (SEM)

	SEM Using Self-Reported Adherence (MARS-5)				SEM Using Claims-Based Adherence (mMPR)			
Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	*P* Value	Odds Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Index drug (weight loss vs. weight gain/neutral)								
Age	1.00	0.98	1.02	0.677	0.99	0.96	1.02	0.494
Sex (female vs. male)	0.88	0.58	1.34	0.545	0.78	0.35	1.75	0.548
Baseline BMI	1.01	0.98	1.05	0.451	1.03	0.97	1.10	0.271
Baseline HbA1c	0.90	0.79	1.03	0.110	1.07	0.83	1.37	0.622
Prior diabetes treatment (number of classes)	**0.25**	**0.18**	**0.35**	**<0.001**	**0.32**	**0.19**	**0.55**	**<0.001**
Comorbidities (number)	1.03	0.88	1.22	0.701	1.09	0.83	1.44	0.526
Adherent vs. nonadherent								
Beliefs (latent variable)	0.85	0.60	1.21	0.359	0.83	0.53	1.30	0.421
Index drug (weight loss vs. weight gain/neutral)	0.80	0.55	1.15	0.227	1.81	0.78	4.20	0.169
Prior drug treatments (number of classes)	1.03	0.99	1.08	0.149	1.01	0.94	1.08	0.815
Weight loss ≥3% (vs. no weight loss)								
Index drug (weight loss vs. weight gain/neutral)	**2.96**	**1.93**	**4.60**	**<0.001**	**3.53**	**1.60**	**7.80**	**0.002**
Prior diabetes treatment (number of classes)	0.91	0.76	1.09	0.299	1.04	0.76	1.43	0.790
Age	1.01	0.99	1.03	0.227	1.02	0.99	1.05	0.170
Sex (female vs. male)	1.12	0.76	1.66	0.573	1.37	0.66	2.84	0.401
Baseline BMI	1.02	1.00	1.05	0.116	1.03	0.98	1.08	0.261
Comorbidities (number)	0.96	0.82	1.12	0.580	0.87	0.64	1.17	0.359
Adherent vs. nonadherent	**1.70**	**1.11**	**2.61**	**0.016**	1.59	0.66	3.83	0.305
HbA1c goal achievement (<7.0% vs. ≥7.0%)								
Age	1.00	0.99	1.02	0.755	1.02	0.99	1.04	0.245
Baseline BMI	0.99	0.97	1.02	0.619	0.99	0.94	1.04	0.704
Baseline HbA1c	**0.71**	**0.62**	**0.82**	**<0.001**	**0.70**	**0.53**	**0.92**	**0.012**
Weight loss ≥3% (vs. no weight loss)	**3.60**	**2.39**	**5.46**	**<0.001**	**2.99**	**1.45**	**6.17**	**0.003**
Adherent vs. nonadherent	**1.59**	**1.09**	**2.34**	**0.018**	**2.70**	**1.22**	**5.98**	**0.014**

Note: Bold numbers represent variables that were significantly associated with the endogenous variable of interest.
BMI = body mass index; CI = confidence interval; HbA1c = hemoglobin A1c; MARS-5 = 5-item Medication Adherence Rating Scale; mMPR = modified medication possession ratio.

Discussion

This historical cohort study of patients with T2DM treated in a managed, integrated care setting confirmed previous studies in finding that weight loss ≥3% was associated with being at HbA1c goal (HbA1c <7.0%) after initiating a newly prescribed class of diabetes medication.[41] Further, this study found that the association between weight loss and glycemic control remained when controlling for medication adherence. Additionally, self-reported adherence to diabetes medication was associated with weight loss ≥3%, while both self-reported and pharmacy claims-based adherence were associated with being at HbA1c goal. The study also identified that patients receiving an oral diabetes medication known to be associated with weight loss were more likely to experience weight loss of ≥3% than those receiving an antidiabetic medication associated with weight gain or weight neutrality. The current study is unique not only in considering the role of adherence in diabetes outcomes, but by adjusting for adherence using both self-reported adherence, a means that providers could use to assess adherence, and claims-based methods, an approach more readily available to payers.

The current study builds upon a previous study that examined the association between weight loss and HbA1c control in treatment-naïve patients with T2DM, initiating treatment in a large national EMR database.[41] The previous study found a significant association between weight loss and glycemic control when adjusting for the weight-effect properties of medications. However, that study only included treatment-naïve patients, did not include patients receiving insulin, and did not capture information and control for the effect of medication adherence on outcomes. The current study therefore builds upon the authors' previous work by incorporating medication adherence into the analyses.

There are several possible reasons why adherence has not been previously incorporated into outcome studies of this nature. These include the fact that measuring and interpreting the impact of medication adherence on outcomes is challenging. For example, adherence to drug therapy is complicated, particularly in patients with chronic diseases, because it involves several components. The components of adherence include drug acquisition, comprehension of instructions, and

memory, which are measured in different ways. Because GHS has access to clinical records and pharmacy claims data, and it has a research infrastructure for contacting patients, the relationship between adherence, weight loss, and glycemic control could be explored in this setting using self-reported and claims-based adherence. The fact that adherence was associated with good glycemic control regardless of the measure used suggests that beneficial outcomes are associated with adherence overall, rather than with specific adherence behaviors. While not specifically designed to determine the association of specific patient behaviors with treatment outcomes, these findings suggest that interventions that address any or all components of nonadherence could help improve outcomes. Further, the 2 measures of adherence were not correlated in this study. However, the data suggest that either method for measuring adherence would be appropriate for health plans and providers to use in assessing the association between adherence and glycemic control in their shared populations.

This study recognizes that patients may have discontinued the index drug prior to the end of the 6-month follow-up period. Because the intent of the study was to examine the effects of the index drug on weight and HbA1c, patients who reported taking the index date drug for at least 30 days were asked to respond to the MARS-5 based on their recollection of the first month of treatment. A key design consideration of this study was then selecting a claims-based adherence measure that would assess adherence during this initial time period. However, many measures of adherence calculated from pharmacy claims do not take into account early discontinuation of the drug. By considering adherence while the patient was obtaining medication fills versus a fixed period of time, the mMPR most closely resembled the way adherence was assessed via the survey.

Limitations

There are several limitations to this study. First, this was an observational study, and the influence of unmeasured confounders on the results is unknown. The data sources used in this study did not include data on other variables known to influence both weight and HbA1c outcomes. Notably, this study could not control for adherence to diet and exercise recommendations, which may be associated with medication adherence and could also influence weight outcomes and glycemic control. There may also be confounding by indication, as the weight loss drug group had a significantly higher proportion of patients who were treatment naïve. This higher number may indicate more severe disease in the weight gain/neutral drug group. Though the SEMs adjusted for number of prior diabetes medications prescribed, there may be some residual confounding by indication related to disease severity.

In addition, self-reported adherence is subject to recall bias, and using MARS-5 in a historical context may have increased this risk. In addition, mMPR is known to report higher rates of adherence than other claims-based measures, such as the proportion of days covered.[21] Further, HbA1c goal attainment was used as the primary outcome, and it may be more difficult for patients with very high HbA1c values at baseline to attain the goal. However, this outcome reflects the goals of clinical practice and what is expected of clinicians in treating most patients.

The generalizability of the results may be limited, as the study included a relatively small number of patients from Pennsylvania from a single integrated health system. A significant majority of the patient population was Caucasian, and the mean baseline weight was higher than has been seen in previous observational studies.[41] GHS also has a diabetes system of care for persons with diabetes that includes expectations that providers will measure HbA1c every 6 months and maintain HbA1c <7.0%, in addition to monitoring and setting targets for other measures, such as cholesterol, blood pressure, urine protein, vaccinations, and smoking status.[42,43] While weight management is not a targeted measure, providers participating in this system of care are probably also counseling patients about the importance of weight control in T2DM. This system of care was well established at the time of the study, and diabetes care was not likely to differ by drug class and thus not likely to bias the effect of drug selection on weight loss. However, provider compliance with the system of care may be reflected in better medication adherence as well as better glycemic control. Finally, this environment may not be representative of care received by patients in other settings.

To be included in the study, patients were required to have a GHS primary care provider, which may indicate that the population had greater continuity of care than the overall population of patients with T2DM. The exclusion of patients who took the drug for less than 1 month may also have introduced a selection bias, particularly with regard to adherence outcomes. However, the primary outcome was HbA1c control at 6 months, and the analysis that was performed may better reflect actual treatment received by patients and the impact of this treatment on glycemic outcomes.

The management of patients with T2DM is an ongoing challenge for payers and providers, with shared goals of improving patient outcomes. The associations between adherence, weight loss, and glycemic control seen in this study of patients treated in a managed care setting underscore the importance of promoting weight loss and improving adherence to help patients achieve glycemic control. Even small amounts of weight loss appear to have a clinically meaningful impact on glycemic control, and the weight-effect properties of diabetes medications can play a role in weight outcomes. Current guidelines recommend using MET first line and, as diabetes is a progressive disease, they also recommend choosing second-line agents and doses to avoid weight gain.[13,44] This study also

suggests that payers and providers can target nonadherent patients for interventions using either self-reported or claims-based adherence with confidence that improving adherence in these patients will likely lead to improved glycemic control. Payers and providers should continue to take an individualized approach to patient care, including making available and appropriately using diabetes medications with a discussion of their weight effects and other potential adverse effects, stressing the importance of adherence to drug regimens, and setting goals for weight management.

Conclusions

This study showed that patients receiving an oral diabetes medication known to be associated with weight loss were more likely to experience weight loss than those receiving an antidiabetic medication associated with weight gain or weight neutrality. Further, this study highlights the importance of weight loss and medication adherence in attaining good glycemic control among persons with T2DM. This information emphasizes the importance of targeted programs to promote adherence and weight management in efforts to help patients with T2DM achieve glycemic control.

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DISCLOSURES

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Study design was created by McAdam-Marx, Wygant, Mukherjee, and Brixner, with assistance from Bellows. Ye and Unni took the lead in data collection, with data interpretation performed by the other authors. Writing and revision of the manuscript came primarily from McAdam-Marx and Bellows, with assistance and input from other authors.

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REFERENCES

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*. 2013;36(4):1033-46. Available at: http://care.diabetesjournals.org/content/36/4/1033.full.pdf. Accessed April 8, 2014.

2. Centers for Disease Control and Prevention. *2011 National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States*. Atlanta, GA: Centers for Disease Control and Prevention; 2011.

3. Centers for Disease Control and Prevention. Prevalence of overweight and obesity among adults with diagnosed diabetes—United States, 1988-1994 and 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2004;53(45):1066-68.

4. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. *PLoS One*. 2012;7(8):e42551. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3415427/pdf/pone.0042551.pdf. Accessed April 8, 2014.

5. Flint AJ, Hu FB, Glynn RJ, et al. Excess weight and the risk of incident coronary heart disease among men and women. *Obesity (Silver Spring)*. 2010;18(2):377-83. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2940230/pdf/nihms231716.pdf. Accessed April 8, 2014.

6. Feldstein AC, Nichols GA, Smith DH, Rosales AG, Perrin N. Weight change and glycemic control after diagnosis of type 2 diabetes. *J Gen Intern Med*. 2008;23(9):1339-45. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2518008/pdf/11606_2008_Article_681.pdf. Accessed April 8, 2014.

7. Feldstein AC, Nichols GA, Smith DH, et al. Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care*. 2008;31(10):1960-65. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2551635/pdf/1960.pdf. Accessed April 8, 2014.

8. Neiberg RH, Wing RR, Bray GA, et al. Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors in the Look AHEAD Study. *Obesity (Silver Spring)*. 2012;20(10):2048-56. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632374/pdf/nihms364170.pdf. Accessed April 8, 2014.

9. Ross SA, Dzida G, Vora J, Khunti K, Kaiser M, Ligthelm RJ. Impact of weight gain on outcomes in type 2 diabetes. *Curr Med Res Opin*. 2011;27(7):1431-38.

10. Schwartz SS, Kohl BA. Glycemic control and weight reduction without causing hypoglycemia: the case for continued safe aggressive care of patients with type 2 diabetes mellitus and avoidance of therapeutic inertia. *Mayo Clin Proc*. 2010;85(12 Suppl):S15-S26. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996166/pdf/mayoclinproc_85_12_suppl_003.pdf. Accessed April 8, 2014.

11. Niswender K. Diabetes and obesity: therapeutic targeting and risk reduction—a complex interplay. *Diabetes Obes Metab*. 2010;12(4):267-87.

12. Pi-Sunyer FX. The impact of weight gain on motivation, compliance, and metabolic control in patients with type 2 diabetes mellitus. *Postgrad Med*. 2009;121(5):94-107. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879281/pdf/nihms197031.pdf. Accessed April 8, 2014.

13. Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: an algorithm for glycemic control. *Endocr Pract*. 2009;15(6):540-59. Available at: http://aace.metapress.com/content/0575046r1758qt67/fulltext.pdf. Accessed April 8, 2014.

14. Brooks AM, Thacker SM. Dapagliflozin for the treatment of type 2 diabetes. *Ann Pharmacother.* 2009;43(7):1286-93.

15. Bosi E, Lucotti P, Setola E, Monti L, Piatti PM. Incretin-based therapies in type 2 diabetes: a review of clinical results. *Diabetes Res Clin Pract.* 2008;82(Suppl 2):S102-S107.

16. Paolisso G, Amato L, Eccellente R, et al. Effect of metformin on food intake in obese subjects. *Eur J Clin Invest.* 1998;28(6):441-46.

17. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med.* 1997;102(1):99-110.

18. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther.* 2011;33(1):74-109.

19. Nagrebetsky A, Griffin S, Kinmonth AL, Sutton S, Craven A, Farmer A. Predictors of suboptimal glycaemic control in type 2 diabetes patients: the role of medication adherence and body mass index in the relationship between glycaemia and age. *Diabetes Res Clin Pract.* 2012;96(2):119-28.

20. Ruelas V, Roybal GM, Lu Y, Goldman D, Peters A. Clinical and behavioral correlates of achieving and maintaining glycemic targets in an underserved population with type 2 diabetes. *Diabetes Care.* 2009;32(1):54-56. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2606830/pdf/54.pdf. Accessed April 8, 2014.

21. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother.* 2006;40(7-8):1280-88.

22. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. *J Am Pharm Assoc (2003).* 2011;51(1):90-94.

23. Steiner JF. Self-reported adherence measures: what do they assess and how should we use them? *Med Care.* 2012;50(12):1011-12.

24. Thorpe CT, Bryson CL, Maciejewski ML, Bosworth HB. Medication acquisition and self-reported adherence in veterans with hypertension. *Med Care.* 2009;47(4):474-81.

25. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care.* 2004;42(7):649-52.

26. Cook CL, Wade WE, Martin BC, Perri M 3rd. Concordance among three self-reported measures of medication adherence and pharmacy refill records. *J Am Pharm Assoc (2003).* 2005;45(2):151-59.

27. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol.* 1997;50(1):105-16.

28. Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. *Pharmacotherapy.* 2006;26(4):483-92.

29. Wetzels GE, Nelemans PJ, Schouten JS, van Wijk BL, Prins MH. All that glisters is not gold: a comparison of electronic monitoring versus filled prescriptions—an observational study. *BMC Health Serv Res.* 2006;6:8. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1386653/pdf/1472-6963-6-8.pdf. Accessed April 8, 2014.

30. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care.* 1999;37(9):846-57.

31. Cohen HW, Shmukler C, Ullman R, Rivera CM, Walker EA. Measurements of medication adherence in diabetic patients with poorly controlled HbA(1c). *Diabet Med.* 2010;27(2):210-16.

32. van de Steeg N, Sielk M, Pentzek M, Bakx C, Altiner A. Drug-adherence questionnaires not valid for patients taking blood-pressure-lowering drugs in a primary health care setting. *J Eval Clin Pract.* 2009;15(3):468-72.

33. Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. *Health Qual Life Outcomes.* 2010;8:99. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2944346/pdf/1477-7525-8-99.pdf. Accessed April 8, 2014.

34. Nau DP, Steinke DT, Williams LK, et al. Adherence analysis using visual analog scale versus claims-based estimation. *Ann Pharmacother.* 2007;41(11):1792-97.

35. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in hypertensive seniors. *Am J Manag Care.* 2009;15(1):59-66. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2728593/pdf/nihms-68741.pdf. Accessed April 8, 2014.

36. Farmer A, Kinmonth AL, Sutton S. Measuring beliefs about taking hypoglycaemic medication among people with type 2 diabetes. *Diabet Med.* 2006;23(3):265-70.

37. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res.* 2000;42(3):241-47.

38. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes (Lond).* 2006;30(3):391-99.

39. Jakicic JM, Otto AD, Lang W, et al. The effect of physical activity on 18-month weight change in overweight adults. *Obesity (Silver Spring).* 2011;19(1):100-109.

40. Kline RB. *Principles and Practice of Structural Equation Modeling.* 2nd ed. New York: Guilford Press; 2005.

41. McAdam-Marx C, Mukherjee J, Bellows BK, et al. Evaluation of the relationship between weight change and glycemic control after initiation of antidiabetic therapy in patients with type 2 diabetes using electronic medical record data. *Diabetes Res Clin Pract.* 2014;103(3):402-11.

42. Weber V, Bloom F, Pierdon S, Wood C. Employing the electronic health record to improve diabetes care: a multifaceted intervention in an integrated delivery system. *J Gen Intern Med.* 2007;23(4):379-82. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359509/pdf/11606_2007_Article_439.pdf. Accessed April 8, 2014.

43. Bloom FJ, Graf T, Anderer T, Stewart WF. Redesign of a diabetes system of care using an all-or-none diabetes bundle to build teamwork and improve intermediate outcomes. *Diabet Spectrum.* 2010;23(3):165-69.

44. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35(6):1364-79. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357214/pdf/1364.pdf. Accessed April 8, 2014.