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Determinants of glycaemic control in a practice setting: the role of weight loss and treatment adherence (The DELTA Study)

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SUMMARY

Aims: Examine the association between weight loss and adherence with glycaemic goal attainment in patients with inadequately controlled T2DM. **Materials and methods:** Patients ≥ 18 years with T2DM from a US integrated health system starting a new class of diabetes medication between 11/1/10 and 4/30/11 (index date) with baseline HbA1c ≥ 7.0% were included in this cohort study. Target HbA1c and weight change were defined at 6-months as HbA1c < 7.0% and ≥ 3% loss in body weight. Patient-reported medication adherence was assessed per the Medication Adherence Reporting Scale. Structural equation modelling was used to describe simultaneous associations between adherence, weight loss and HbA1c goal attainment. **Results:** Inclusion criteria were met by 477 patients; mean (SD) age 59.1 (11.6) years; 50.9% were female; 30.4% were treatment naïve; baseline HbA1c 8.6% (1.6); weight 102.0 kg (23.0). Most patients (67.9%) reported being adherent to the index diabetes medication. At 6 months mean weight change was −1.3 (5.1) kg (p = 0.39); 28.1% had weight loss of ≥ 3%. Mean HbA1c change was −1.2% (1.8) (p< 0.001); 42.8% attained HbA1c goal. Adherent patients (OR 1.70; p = 0.02) and diabetes therapies that lead to weight loss (metformin, GLP-1) were associated with weight loss ≥ 3% (OR 2.96; p< 0.001). Weight loss (OR 3.60; p < 0.001) and adherence (OR 1.59; p < 0.001) were associated with HbA1c goal attainment. **Conclusions:** Weight loss ≥ 3% and medication adherence were associated with HbA1c goal attainment in T2DM; weight loss was a stronger predictor of goal attainment than medication adherence in this study population. It is important to consider weight-effect properties, in addition to patient-centric adherence counselling, when prescribing diabetes therapy.

What's known

- Diabetes-related complications are reduced in patients with type 2 diabetes that have good glycemic control.
- In patients with type 2 diabetes, weight loss significantly improves glycemic control.
- Patients that are adherent to diabetes medication regimens have better glycemic control than non-adherent patients.

What's new

- When considered simultaneously, weight loss and adherence were associated with good glycemic control though weight loss was the strongest predictor in this population.
- Structural equation model is a valuable tool to examine complex associations between patient characteristics and treatment outcomes in diabetes.

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Introduction

Type 2 diabetes, which is characterised by increased insulin resistance resulting in increased production of insulin, hyperinsulinemia and eventually pancreatic beta cell failure (1,2), is a major public health concern. In the USA, type 2 diabetes affects over 25 million individuals at a societal cost of $254 billion (3,4). In addition, 85% of patients with type 2 diabetes are overweight or obese, and both conditions are associated with poor cardiovascular outcomes (5,6).

In patients with type 2 diabetes, weight loss has been shown to improve glycaemic control as well as lipid levels and blood pressure (7). For these reasons, effective weight management has come to the forefront of appropriate type 2 diabetes therapy (1,8). However, weight management is a difficult component of treating type 2 diabetes as it is affected by many factors including adherence to diet and lifestyle modifications. In addition, certain diabetes medications increase circulating insulin and are associated with weight gain (9). Regardless of the challenges patients face in losing weight and keeping it off, relatively small amounts of weight loss, as little as 1 kg, have been associated with improved glycaemic control (10). The relationship between weight loss and glycaemic improvement has been seen in several observational studies as well (11–13).

In addition to weight management, another complicating factor in attaining diabetes treatment-

related goals is poor medication adherence (14). Non-adherence has been associated with poor clinical outcomes in diabetes and can influence the magnitude of the treatment effect (15,16). For instance, one study found that patients who were ≥ 80% adherent to their diabetes therapy, as measured by medication event monitoring systems, had lower follow-up HbA1c levels than those who were less adherent (17). However, medication adherence is complex, involves multiple patient behavioural components, and is affected by many factors including medication side effects and cost (18,19).

While diabetes medication adherence is important in helping patients with type 2 diabetes achieve glycaemic goals, it may also result in undesired weight gain in certain classes of diabetes medications. Previous observational research of weight management and glycaemic control has not considered the potential for medication adherence to have a confounding effect on this relationship. The purpose of this study was to explore the relationships between weight change and glycaemic control while also considering how medication adherence affects these treatment-related outcomes in patients with type 2 diabetes treated in an integrated health system in the USA.

Materials and methods

Patients and data

This study included a cohort of adult patients (age ≥ 18 years) with type 2 diabetes treated in the Geisinger Health System (GHS) and with a Geisinger Clinic primary care physician. GHS is an integrated health system in central Pennsylvania that serves over 3 million patients and is comprised of over 880 physicians. GHS has adopted a diabetes system of care that includes the expectation that providers measure HbA1c every 6 months and maintain goal HbA1c, which at the time of the study was < 7.0% for all patients, in addition to other diabetes-related monitoring and treatment targets (20,21). This diabetes system of care does not include a specific measure for weight management.

De-identified electronic medical record (EMR) data including lab results, vital signs, prescription orders, and diagnosis codes were used for this study. Because of the limitations of EMR data, which do not contain prescription fill data, medication adherence was estimated using self-reported adherence obtained via telephone survey from a randomly identified subset of study patients. Adherence was measured using the 5-item Medication Adherence Report Scale (MARS-5) (22), which has been used previously in diabetes (see Appendix for full MARS-5 questionnaire) (17,19,23). Through additional questions developed by the research team, patients were asked to report their beliefs and perceptions regarding treatment-related weight changes. The study protocol and survey were reviewed and approved by the Institutional Review Boards at the University of Utah and GHS.

Patients were included in the study if they were treated with a diabetes medication from a class not previously prescribed for that patient between November 1, 2010 and April 30, 2011. The date of the prescription order for that newly prescribed diabetes medication was considered the index date. Diabetes medications were grouped according to weight-effect properties as recognised by the literature. Diabetes medications were considered as either associated with weight loss [glucagon-like peptide-1 agonists (GLP-1) and metformin (MET)] or not generally associated with weight loss [sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4) or insulin (INS)] (9,24,25). Other agents (meglitinides, pramlintide or α-glucosidase inhibitors) were grouped as a miscellaneous class as in aggregate they represented < 5% of index date medications, and were included with the weight gain/weight neutral diabetes medications based on the weight effects of the majority of the agents in this grouping.

Patients were excluded if they had type 1 diabetes, if they were prescribed more than one new diabetes class on index day, if they had a diagnosis for dementia or other cognitive impairment that may have interfered with their ability to answer survey questions, or if they resided in a nursing home. The final analysis was performed on surveyed patients with a baseline HbA1c ≥ 7%.

The primary treatment outcome of the study was defined *a priori* as HbA1c goal attainment (HbA1c < 7.0%). Weight loss, which was considered an outcome of treatment as well as a predictor of glycaemic control, was defined *a priori* as a loss of body weight of ≥ 3% from baseline as reported in the EMR 6 months after index date. For descriptive purposes, weight change categories of weight gain (weight gain of ≥ 3%) and weight neutral (weight change < 3%) were also included. While modest, a change in body weight of at least 3% is considered to be clinically meaningful and not likely because of measurement error or normal weight fluctuation (26,27). Though a 5% or 7% change in weight is often viewed as clinically significant when examining weight loss interventions in clinical trials, the current study was not examining a specific weight loss intervention. Thus, as the authors have done previously, a 3% threshold was used and considered to be clinically meaningful (28).

As a quantified measure of medication adherence is not available in EMR data, patients were randomly selected to participate in a telephone survey to assess adherence to the index date medication. Patients were contacted approximately 9–15 months after starting the index medication. Patients were invited to participate in the survey until 600 agreed. Self-reported adherence was assessed using the MARS-5 adherence scale (22). As was determined *a priori*, patients were considered adherent to therapy if they reported that they never missed or altered a medication dose for each of the five questions, an approach consistent with previous studies (23,29). While 600 patients were surveyed, patients were not included in the analysis if they reported never taking the index date medication or taking it for less than 1 month as this would not accurately reflect the impact of the medication on 6-month HbA1c outcomes.

Statistical analyses

Weight and HbA1c outcomes were reported overall and stratified by drug class and adherence. A structural equation model (SEM) was developed to simultaneously assess the associations between baseline characteristics, index date diabetes drug class, self-reported adherence, weight changes and HbA1c goal attainment considering patient medication beliefs and perceptions (Figure 1). SEM allows for the simultaneous examination of multiple endogenous variables (similar to dependent or outcome variables) from multiple exogenous variables (similar to independent variables) and latent variables (not directly measured in the data) (30). In addition, endogenous/outcome variables, such as weight loss, can be outcomes as well as predictors of other endogenous/outcome variables, such as attainment of good glycaemic control. This approach differs from logistic or linear regression techniques as they are only able to consider one outcome variable at a time. An SEM was deemed appropriate for this study because multiple outcomes (i.e., weight change and HbA1c), were being considered, as was the association between the two outcomes. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and Mplus 6.11 (Muthen & Muthen, Los Angeles, CA).

Results

A total of 1080 patients met the inclusion criteria and were included in the dataset; and of these 600 participated in the adherence survey. There were no apparent differences in the characteristics of patients that responded to the survey when compared with those who did not (results not shown). The final study cohort was comprised of 477 patients with self-reported data on medication adherence and a baseline HbA1c of ≥ 7% (Figure 2). Baseline characteristics of the study cohort by weight-effect properties of the prescribed index date diabetes medication are provided in Table 1. Overall, the mean (SD) age was 59.1 (11.6) years and 49.1% were female. The mean baseline HbA1c was 8.6% (1.6), mean baseline weight was 102.0 (23.0) kg, and 30.4% were diabetes treatment naïve. A total of 67.9% of patients reported being adherent to the prescribed diabetes medication (Table 2).

At 6 months post-index date, the mean change in weight observed in the cohort was −1.3 (5.6) kg with 28.1% losing weight, 55.1% remaining weight stable and 16.8% gaining weight. Of the patients on weight loss diabetes medications, 8.8% gained weight while 45.3% lost weight. In contrast, of the patients treated

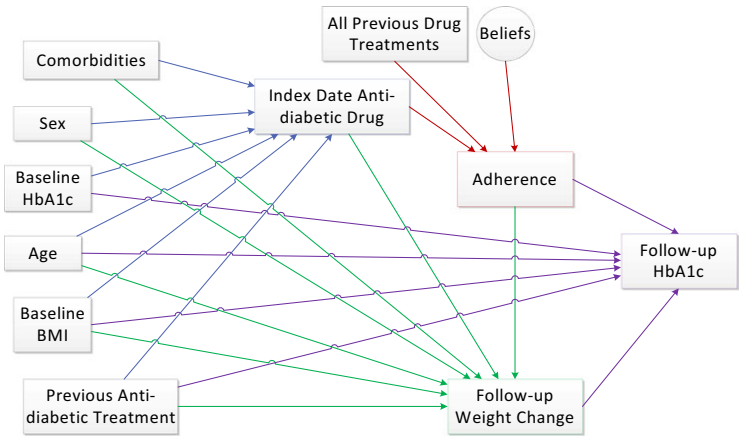

Figure 1 Structural equation model (SEM) diagram. This figure shows the associations examined in the SEM. In the diagram, endogenous variables are predicted by other variables, exogenous variables are not predicted by any other variables, and latent variables are represented as circles

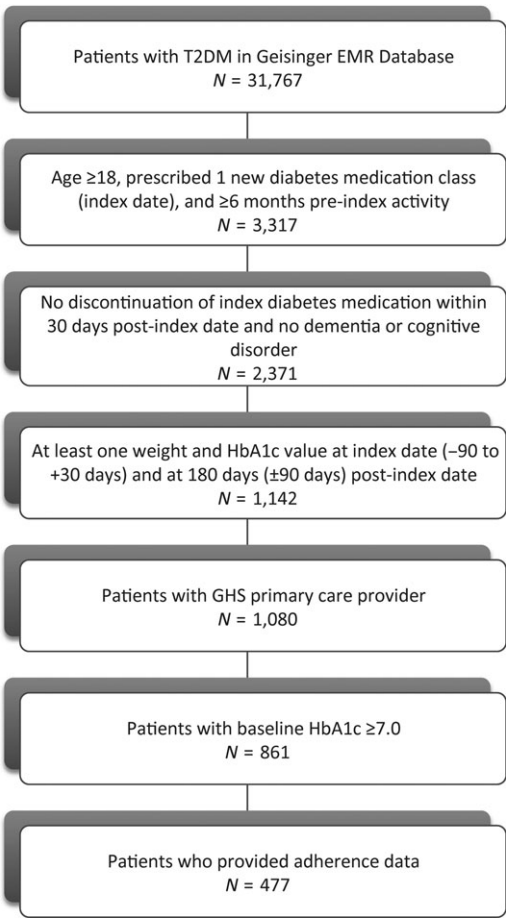

Figure 2 Patient identification flow chart. T2DM, type 2 diabetes mellitus; EMR, electronic medical record; GHS, Geisinger Health System

with weight gain/neutral diabetes drugs, 21.2% gained weight and 18.5% lost weight. A greater proportion of adherent patients than non-adherent patients lost weight in each drug class (Table 2).

The overall mean change in HbA1c was −1.2% (1.77) with 42.8% of patients attaining HbA1c < 7.0% at 6 months. Of patients who lost ≥ 3% of body weight, 64.2% reached HbA1c goal, compared with 33.1% who remained weight stable and 38.8% who gained weight ($p < 0.001$). Adherent patients had a mean change in HbA1c of −1.3% and non-adherent patients had a change in HbA1c of −1.1% ($p = 0.26$). Overall, of patients who reported to be adherent, 47.5% reached HbA1c goal vs. 32.7% of patients who reported to be non-adherent ($p = 0.002$). In addition, a greater proportion of adherent patients attained goal compared with non-adherent patients in each drug class except for patients in the miscellaneous category (Table 2).

The SEM showed that patients on diabetes medications known to cause weight loss (MET/GLP-1), were more likely to lose ≥ 3% of body weight than those on diabetes medications not generally associated with weight loss [OR 3.07 (95% CI 1.91, 4.94)]. There was a trend for patients who were adherent to be more likely to lose weight (OR = 1.56; 95% CI: 0.97, 2.49), but this trend did not reach significance ($p = 0.06$).

In terms of attaining HbA1c goal, patients were less likely to attain goal if they had a higher baseline HbA1c [OR 0.85 (95% CI 0.74, 0.98)] or were prescribed diabetes medication classes prior to index date [OR 0.67 (95% CI 0.57, 0.79)] than those with lower baseline HbA1c or who were treatment naïve (Table 3). However, patients who lost ≥ 3% of body weight [OR 3.02 (95% CI 1.94, 4.70)] and adherent patients [OR 1.90 (95% CI 1.23, 2.93)] were more likely to attain HbA1c goal than those who gained weight or who were not adherent.

Discussion

This observational study of patients treated in an integrated health system with uncontrolled type 2 diabetes found that weight loss of ≥ 3% after initiation of new therapy and adherence to diabetes medication therapy were both associated with HbA1c goal attainment (< 7.0%). Of these two factors, weight loss was the stronger predictor of attaining HbA1c goal. Factors simultaneously predicting weight loss included being prescribed diabetes medications with weight loss properties and medication adherence.

This study is unique in simultaneously assessing the association of both adherence and weight loss with the attainment of good glycaemic control vs. assessing these associations separately, thereby providing a more comprehensive real-world assessment of these relationships. By using an SEM, this study was able to assess some of the complex relationships that exist when treating patients with type 2 diabetes. For example, the SEM was able to assess the effect baseline HbA1c and prior diabetes treatment had on both treatment selection and ability to attain glycaemic control. This more accurately reflects real-world treatment decisions and the influence they have on outcomes. Furthermore, the technique used in this study accurately reflects that weight loss is both a treatment outcome and a predictor of HbA1c outcomes.

This study showed that medication adherence is associated with both weight loss and HbA1c goal. The results of this study emphasise that weight loss in patients with type 2 diabetes, as is stressed in the current treatment guidelines (9,31), is critical as both a desired treatment outcome and also as a facilitator of glycaemic control. Therefore, this study highlights

Table 1 Baseline characteristics of study population stratified by index drug group (n = 477)

	Overall (N = 477)		MET/GLP-1 (N = 170)		SU/TZD/DPP-4/INS/ Other (N = 307)		
	N/Mean	%/SD	*N*/Mean	%/SD	*N*/Mean	%/SD	p-Value
Demographics							
Age							
Mean (SD)	59.1	11.6	58.4	11.7	59.5	11.5	0.31
Age group							
< 65	322	67.5	117	68.8	205	66.8	0.65
≥ 65	155	32.5	53	31.2	102	33.2	
Sex							
Male	234	49.1	91	53.5	143	46.6	0.15
Female	243	50.9	79	46.5	164	53.4	
Race							
Caucasian	461	96.6	164	96.5	297	96.7	0.49
African–American	14	2.9	6	3.5	8	2.6	
Other	2	0.4	0	0.0	2	0.7	
Clinical characteristics							
Baseline weight, mean (SD)	102	23.0	102	21.0	101.9	24.1	0.99
Baseline BMI, mean (SD)	35.8	7.4	35.8	6.9	35.8	7.7	0.98
Baseline HbA1c, Mean (SD)	8.6	1.6	8.4	1.6	8.7	1.7	0.08
Comorbidities							
Coronary heart disease	111	23.3	41	24.1	70	22.8	0.74
Chronic kidney disease	181	37.9	40	23.5	141	45.9	< 0.001
Hypertension	393	82.4	130	76.5	263	85.7	0.01
Dyslipidaemia	444	93.1	158	92.9	286	93.2	0.93
Cerebrovascular disease	32	6.7	11	6.5	21	6.8	0.88
Stroke	5	1.0	1	0.6	4	1.3	0.46
Myocardial infarction	12	2.5	6	3.5	6	2.0	0.29
Microvascular complications	74	15.5	15	8.8	59	19.2	0.003
Thyroid disease	98	20.5	35	20.6	63	20.5	0.99
Depression	83	17.4	24	14.1	59	19.2	0.16
Non-alcoholic fatty liver disease	18	3.8	5	2.9	13	4.2	0.48
Number of prior diabetes medication antidiabetic drug classes used							
0	145	30.4	121	71.2	24	7.8	< 0.001
1	114	23.9	20	11.8	94	30.6	< 0.001
2	126	26.4	19	11.2	107	34.9	< 0.001
3	62	13	7	4.1	55	17.9	< 0.001
≥ 4	30	6.3	3	1.8	27	8.8	< 0.001

MET, metformin; GLP-1, glucagon-like peptide-1 agonist; SU, sulfonylurea; TZD, thiazolidinedione; DPP-4, dipeptidylpeptidase-4 inhibitor; INS, insulin.

the importance of aligning medication weight change properties and treatment effectiveness profiles with established treatment goals. It also serves as a reminder of the importance of making diabetes treatment decisions that address patient treatment expectations and concerns about treatment-related weight gain and other adverse effects, essential factors in helping patients remain compliant with diabetes therapy.

The current study was built upon a prior study that also found a significant correlation between weight loss and HbA1c goal attainment (13). However, the prior study only included treatment-naïve patients, did not include patients initiating treatment with insulin, and was unable to capture information on medication adherence. The current study addresses these limitations by including non-treatment-naïve patients and those on insulin as well as measuring diabetes medication adherence.

The findings in the current study are also consistent with other studies, including the Look AHEAD trial, which found that patients with diabetes who lost weight had better glycaemic control outcomes and required fewer medications to manage their diabetes (32,33). Self-reported adherence to the pre-

Table 2 Adherence, weight, and HbA1c outcomes at 6 months follow-up

		Weight loss drugs		Weight gain/neutral drugs				
	Overall (*N* = 477)	MET (*N* = 159)	GLP-1 (*N* = 11)	SU (*N* = 105)	TZD (*N* = 27)	DPP-4 (*N* = 71)	INS (*N* = 82)	Other (*N* = 22)
Adherent (MARS-5 = 25)								
N	324	102	6	79	21	53	51	12
%	67.9	64.2	54.5	75.2	77.8	74.6	62.2	54.5
Median weight change (kg)	−0.9	−2.7	−2.3	0.0	0.9	−0.5	−0.5	−1.4
% Losing ≥ 3% Body Weight	29.9	47.1	50.0	16.5	23.8	20.8	27.5	25.0
Mean HbA1c change (%)	−1.3	−1.5	−0.9	−1.2	−1.4	−0.8	−1.7	0.2
% Achieving HbA1c < 7%	47.5	56.9	16.7	54.4	57.1	39.6	35.3	8.3
Non-adherent (MARS-5 < 25)								
N	153	57	5	26	6	18	31	10
%	32.1	35.8	45.5	24.8	22.2	25.4	37.8	45.5
Median weight change	−0.9	−2.3	−2.3	0.0	0.0	0.9	−0.9	−0.2
% Losing ≥ 3% Body Weight	24.2	42.1	40.0	11.5	16.7	16.7	12.9	0.0
Mean HbA1c Change	−1.1	−1.3	−1.1	−1.2	−0.4	−0.3	−1.5	−0.5
% Achieving HbA1c < 7%	32.7	50.9	0.0	26.9	33.3	16.7	19.4	30.0

MET, metformin; GLP-1, glucagon-like peptide-1 agonist; SU, sulfonylurea; TZD, thiazolidinedione; DPP-4, dipeptidylpeptidase-4 inhibitor; INS, insulin; MARS-5, Medication Adherence Report Scale.

Table 3 Results of the structural equation model (SEM)

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Index Drug (MET/GLP-1 vs. any other class)				
Age	1.00	0.98	1.02	0.87
Sex (Female vs. Male)	0.82	0.53	1.28	0.39
Baseline BMI	1.00	0.97	1.04	0.94
Baseline HbA1c	0.93	0.80	1.08	0.35
Prior diabetes treatment (# of classes)	0.28	0.19	0.40	< 0.001
Comorbidities (# of comorbidities)	1.01	0.84	1.22	0.93
Index Date Adherence (MARS-5: 25 vs. < 25)				
Medication beliefs and perceptions (latent variable)	0.75	0.46	1.20	0.23
Index drug (MET/GLP-1 vs. any other class)	0.77	0.51	1.15	0.20
Prior drug treatments (# of classes)	1.03	0.98	1.08	0.27
Weight loss ≥ 3% (vs. no weight loss)				
Index drug (MET/GLP-1 vs. any other class)	3.07	1.91	4.94	< 0.001
Prior diabetes treatment (# of classes)	0.85	0.69	1.06	0.15
Age	1.00	0.98	1.02	0.84
Sex (Female vs. Male)	1.21	0.78	1.88	0.39
Baseline BMI	1.02	0.99	1.05	0.19
Comorbidities (# of comorbidities)	0.94	0.78	1.12	0.46
Index Date Adherence (MARS-5: 25 vs. < 25)	1.56	0.97	2.49	0.06
HbA1c goal achievement (< 7% vs. ≥ 7%)				
Age	1.01	0.99	1.03	0.46
Baseline BMI	1.00	0.97	1.03	0.88
Baseline HbA1c	0.85	0.74	0.98	0.02
Weight loss ≥ 3% (vs. no weight loss)	3.02	1.94	4.70	< 0.001
Prior diabetes treatment (# of classes)	0.67	0.57	0.79	< 0.001
Index Date Adherence (MARS-5: 25 vs. < 25)	1.90	1.23	2.93	0.004

MET, metformin; GLP-1, glucagon-like peptide-1 agonist; SU, sulfonylurea; TZD, thiazolidinedione; DPP-4, dipeptidylpeptidase-4 inhibitor; INS, insulin.

scribed diabetes medication was also similar to other studies of patients with diabetes (34). For many, these associations may seem intuitive. However, this is the first real-world study to our knowledge to examine the association between two treatment-related outcomes, weight loss and HbA1c goal attainment, while also examining how medication adherence, a common barrier to optimal diabetes management, influences these outcomes.

This study found that good self-reported adherence is associated with improved glycaemic control. However, adherence is multifaceted and the reasons for medication non-adherence are complex and driven by many factors including ability to pay, patient–provider relationships and communication, medical conditions, complexity of drug therapy and patient knowledge and beliefs about their illness and treatment (35). Some of these factors, such as ability to pay and patient–provider communications, could not be captured in this study. Further, non-adherence can be unintentional or intentional, a distinction that is an important but challenging aspect of diabetes patient care. Self-reported measures remain the most practical way for clinicians to assess medication adherence during a patient visit, although there is limited information regarding the most appropriate and reliable scale to use in the clinic setting (36). However, published guidance on addressing medication adherence recognise the importance of engaging patients in patient-centric solutions based vs. blame-based dialogue (37). A key area of this guidance is recognition and communication regarding a patient's medication-related concerns. In the case of diabetes therapy, these concerns may be related to side effects, including weight gain.

This study also found that weight loss was associated with improved glycaemic control when controlling for medication adherence and other patient characteristics. Weight management is a difficult component of treating type 2 diabetes and current guidelines recommend weight loss of 7% of body weight (38). While a $\geq$ 3% weight loss was used in this study, a *post hoc* analysis was performed to examine the effects with a $\geq$ 5% weight loss and found similar results (39). Therefore, this study adds to the body of evidence that even relatively small weight loss in patients with type 2 diabetes can have a meaningful impact on glycaemic control.

This study also has several limitations that need to be acknowledged. This study included both treatment-experienced and treatment-naïve patients, which has the potential to introduce bias because of disease severity. Furthermore, more treatment-naïve patients received weight loss diabetes medications than treatment-experienced patients. However, the SEM, which is a multivariate method, controlled for prior diabetes medication use in examining the association of weight loss and HbA1c goal attainment. An additional concern is that lifestyle behaviours such as diet and exercise were not captured in the EMR database in a manner that could be queried and were not addressed in the patient survey. Although diet and exercise are known to reduce weight and HbA1c, the extent to which they impacted outcomes in this study remains unknown. In addition, the influence of other unobserved confounders related to diabetes medication classes and glycaemic control (e.g. other metabolic factors, incretin levels, insulin secretion and resistance and inflammation) remains unknown.

In a related issue, the GHS diabetes system of care, which was implemented in 2006, likely contributed to the overall treatment effects seen in this study cohort, as providers may deliver care that differs from the usual care received by patients with diabetes outside of GHS. For instance, patients in this study cohort, on average, lost weight during the study period. This was not a trend expected in a population of patients with type 2 diabetes, or uniquely anticipated for this population as weight management is not a defined component of the GHS diabetes system of care. Nonetheless, the observed changes in glycaemic control and weight may reflect a combination of drug therapy and education-based interventions that may have increased the observed effect size. While it can be theorised that this system of care would influence outcomes similarly by drug class, if patients differ by class in their self-management activities or if provider adherence to the system of care varies by prescribed class, study findings could be biased. In addition, formulary restrictions within GHS may limit access to certain diabetes medication classes and skew results or provide minimal sample size.

Recall bias may have been introduced into the study as a portion of data used was collected from patients during the survey. Patients in the study were surveyed between 9 and 15 months after starting the index date medication and this may have caused patients to either over- or underestimate adherence. Notably, a higher proportion of patients were classified as adherent on the MARS-5 when asked to think back to when they started the index date medication compared with when asked about how they take their current regimen (67.9% vs. 49.3%, respectively). While this may reflect better adherence when a class of drug is first initiated, it may also reflect a tendency for patients to overestimate past adherence.

Ongoing research, using the subset of surveyed patients that have insurance through the Geisinger Health Plan, will also examine adherence using prescription claims data and will thus eliminate the risk of recall bias. It is also possible that patients switched drug regimens between the time survey occurred and when the index drug was taken. However, nearly 92% of survey respondents reported taking the index drug for more than 3 months. Thus, while the impact of drug switches remains unknown, it is unlikely to have had a large impact on the glycaemic outcomes at 6 months after starting the index drug as the vast majority took the index drug for at least 3 months.

Moreover, patients were asked about diabetes medication adherence when starting the drug, but adherence is not static and actual adherence for patients in both groups may have varied across the study period. Another related concern is that patients who responded to the survey were showing a willingness to comply with the study and may also be more likely to be adherent. The survey had a relatively high participation rate (58%) and the characteristics of patients, who did and did not participate were similar (data not shown). Though the differences in adherence between those who participated and those who did not participate are likely to be small, the actual impact remains unknown. Also related to adherence, patients were grouped as adherent and non-adherent according to their MARS-5 score. However, the MARS-5 questionnaire was not developed to provide a cut-off for adherent and less adherent patients and the cut-offs used have varied between studies (18,23,29).

The generalisability of this study may be limited because of the population included. GHS is located in central Pennsylvania and largely consists of patients from a rural area with over 96% of the population being Caucasian. Further, the BMI of the study cohort was high (35.8 kg/m^2) relative to the USA diabetes population (32.2 kg/m^2) (40). However, the BMI of this cohort was similar to patients in retrospective study of patients in a different integrated health system (36.1 kg/m^2) (41). The patients included in this study were also required to have a GHS primary care provider, which may introduce selection bias for patients who are actively seeking care.

In conclusion, weight loss $\geq$ 3% and medication adherence were associated with HbA1c goal attainment (< 7.0%) in a population of patients with type 2 diabetes treated by an integrated health system. Both are important management considerations; however weight loss appears to have a stronger association with HbA1c goal attainment than medication adherence. These findings further highlight the importance of weight loss in patients with type 2 diabetes. This includes a consideration of factors influencing weight change, including diabetes medication weight properties and patient-centric adherence counselling, when prescribing diabetes medications.

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Author contributions

CMM, BKB and SU were responsible for the conception and design of the study, the interpretation of the results, and drafting, revising and approving the manuscript. JM, GW, UI and DIB were responsible for the conception of the study, interpretation of the results, and revising and approving the manuscript. JNL was responsible for design of the study, interpretation of the results, and revising and approving the manuscript. XY was responsible for the design of the study, analysis, interpretation of the results and approving the final manuscript. FJB was responsible for interpretation of the results as well as revising and approving the manuscript.

References

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

2 Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. *Diabetes Res Clin Pract* 2011; **93**(Suppl. 1): S52–9.

3 Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States*, 2011. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

4 American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013; **36**(4): 1033–46.

5 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.

6 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.

7 Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. *J Am Coll Nutr* 2003; **22**(5): 331–9.

8 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.): S15–26.
9 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.
10 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): 1431–8.
11 Chaudhry ZW, Gannon MC, Nuttall FQ. Stability of body weight in type 2 diabetes. *Diabetes Care* 2006; **29**(3): 493–7.
12 Feldstein AC, Nichols GA, Smith DH et al. Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care* 2008; **31**(10): 1960–5.
13 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, 2014. http://dx.doi.org/10.1016/j.diabres.2013.12.038 (accessed July 29, 2013).
14 Grant R, Adams AS, Trinacty CM et al. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. *Diabetes Care* 2007; **30**(4): 807–12.
15 Chen CC, Tseng CH, Cheng SH. Continuity of care, medication adherence, and health care outcomes among patients with newly diagnosed type 2 diabetes: a longitudinal analysis. *Med Care* 2013; **51**(3): 231–7.
16 Kim MY, Suh S, Jin SM et al. Education as prescription for patients with type 2 diabetes mellitus: compliance and efficacy in clinical practice. *Diabetes Metab J* 2012; **36**(6): 452–9.
17 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.
18 Borgsteede SD, Westerman MJ, Kok IL, Meeuse JC, de Vries TP, Hugtenburg JG. Factors related to high and low levels of drug adherence according to patients with type 2 diabetes. *Int J Clin Pharm* 2011; **33**(5): 779–87.
19 French DP, Wade AN, Farmer AJ. Predicting self-care behaviours of patients with type 2 diabetes: the importance of beliefs about behaviour, not just beliefs about illness. *J Psychosom Res* 2013; **74**(4): 327–33.
20 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* 2008; **23**(4): 379–82.
21 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. *Diabetes Spectr* 2010; **23**(3): 165–9.
22 Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999; **47**(6): 555–67.
23 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.
24 Paolisso G, Amato L, Eccellente R et al. Effect of metformin on food intake in obese subjects. *Eur J Clin Invest* 1998; **28**(6): 441–6.
25 Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med* 1997; **102**(1): 99–110.
26 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): 100–9.
27 Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes (Lond)* 2006; **30**(3): 391–9.
28 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.
29 Gialamas A, Yelland LN, Ryan P et al. Does point-of-care testing lead to the same or better adherence to medication? A randomised controlled trial: the PoCT in General Practice Trial. *Med J Australia* 2009; **191**(9): 487–91.
30 Kline RB. Core SEM Techniques and Software. In: Kenny DA, ed. *Principles and Practice of Structural Equation Modeling*, 2nd edn. New York, NY: Guilford Press, 2005: page 63–90.
31 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.
32 Redmon JB, Bertoni AG, Connelly S et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care* 2010; **33**(6): 1153–8.
33 Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010; **170**(17): 1566–75.
34 Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008; **28**(4): 437–43.
35 World Health Organization. Adherence to long-term therapies: evidence for action, 2003. http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf (accessed July 29, 2013)
36 Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. *BMC Med Res Methodol* 2011; **11**: 149.
37 National Institute for Health and Clinical Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence, 2009. http://www.nice.org.uk/nicemedia/live/11766/43042/43042.pdf.(accessed July 29, 2013)
38 American Diabetes Association. Standards of medical care in diabetes – 2013. *Diabetes Care* 2013; **36** (Suppl. 1): S11–66.
39 McAdam-Marx C, Bellows BK, Wygant G et al. Association of >5% weight loss and self-reported adherence with 6-month glycemic control in type 2 diabetes mellitus (T2DM): the DELTA Study. *Diabetes* 2013; **62**(Suppl. 1): A217–364.
40 Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? *Diabetes Care* 2008; **31**(1): 81–6.
41 Nichols GA, Alexander CM, Girman CJ, Kamal-Bahl SJ, Brown JB. Treatment escalation and rise in HbA1c following successful initial metformin therapy. *Diabetes Care* 2006; **29**(3): 504–9.

Appendix: 5-item Medication Adherence Report Scale (MARS-5)

1 I forgot to take my diabetes medicines
2 I altered the dose of my diabetes medicines
3 I stopped taking my diabetes medicine for a while
4 I decided to miss out a dose of my diabetes medicine
5 I took less diabetes medicine than instructed

Patients answer each question with:

Always = 1 point
Often = 2 points
Sometimes = 3 points
Rarely = 4 points
Never = 5 points

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