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Association of Weight Loss and Medication Adherence Among Adults With Type 2 Diabetes Mellitus: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes)☆

Susan Grandy, PhD[1], Kathleen M. Fox, PhD[2,*], Elise Hardy, MD[1], for the SHIELD Study Group

[1] AstraZeneca LP, Wilmington, Delaware
[2] Strategic Healthcare Solutions, LLC, Monkton, Maryland

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ABSTRACT

Background: Adherence to prescribed diabetes medications is suboptimal, which can lead to poor glycemic control and diabetic complications. Treatment-related weight gain is a side effect of some oral antidiabetic agents and insulin, which may negatively affect adherence to therapy.
Objective: This study investigated whether adults with type 2 diabetes mellitus (T2DM) who lost weight had better medication adherence than those who gained weight.
Methods: Weight change over 1 year (2007 to 2008) was assessed among respondents in the US Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Weight loss of $>1.0\%$, $\geq 3\%$, and $\geq 5\%$ of weight was compared with weight gain of $\geq 1.0\%$. Medication adherence was assessed using the Morisky 4-item questionnaire for medication-taking behavior, with lower scores representing better adherence.
Results: There were 746 T2DM respondents who lost $>1.0\%$, 483 who lost $\geq 3\%$, 310 who lost $\geq 5\%$, and 670 who gained $\geq 1.0\%$ of weight. Each weight-loss group had significantly lower Morisky scores than the weight-gain group; mean scores of 0.389 versus 0.473 ($P = 0.050$) for the $>1.0\%$ weight-loss group, 0.365 versus 0.473 ($P = 0.026$) for the $\geq 3\%$ weight-loss group, and 0.334 versus 0.473 ($P = 0.014$) for the $\geq 5\%$ weight-loss group. Significantly fewer respondents who lost weight had received insulin, sulfonylurea, or thiazolidinedione therapy (57%) compared with respondents who gained weight (64%) ($P = 0.002$). Demographics, exercise habits, and dieting were similar between weight-loss and weight-gain groups.
Conclusions: T2DM respondents with weight loss had significantly better medication adherence and were less likely to be on treatment regimens that increase weight than T2DM respondents with weight gain. These findings suggest that strategies that lead to weight loss, including use of diabetes medications associated with weight loss, may improve medication adherence.

Introduction

Patient adherence to prescribed therapies in type 2 diabetes mellitus (T2DM) including lifestyle changes and medications, is of substantial importance. With the large and increasing number of patients affected by T2DM and the associated disease and economic burden to patients, payers, and employers,[1,2] there is a need to improve outcomes and reduce costs. Among patients with type 2 diabetes, adherence to prescribed medications has been reported to be 60% or lower, indicating that many patients are not following the treatment plan and receiving the full clinical benefit of the therapies.[3–5] Poor adherence can compromise safety and treatment effectiveness, leading to increased mortality and morbidity.[6,7] Conversely, better medication adherence would promote better outcomes. Improvement in adherence has been shown to improve glycemic control[3,8]; in 1 study, glycated hemoglobin (HbA_{1c}) was reduced by 0.34% for every 25% increase in medication adherence.[9] In a study of 301 patients, good adherence assessed by the Morisky survey was associated with a 10% lower HbA_{1c} adjusted for patient demographics and clinical characteristics.[10] Greater medication adherence was associated with lower rates of hospitalization and lower health care costs.[11] One study

* Address correspondence to: Kathleen M. Fox, PhD, PO Box 543, Monkton, MD 21111.
E-mail address: kathyfox@gforcecable.com (K.M. Fox).

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observed an 8.6% decrease in annual total health care costs for every 10% increase in medication possession ratio.[12] In a US sample of patients with T2DM from 2005 to 2008, improved adherence was associated with 13% lower odds of subsequent hospitalizations or emergency department visits, which projected to averting 699,000 emergency department visits and 341,000 hospitalizations annually, for a savings of $4.7 billion.[13] Adherent employees with diabetes had between 1.7 and 7.1 fewer days absent from work and between 1.1 and 5.0 fewer days on short-term disability in a health care claims study.[14]

The majority of patients with T2DM are overweight or obese,[15,16] and increased weight has been shown to worsen glycemic control and increase the risk of diabetes progression.[17,18] Additionally, weight loss has been shown in large clinical trials to significantly improve glycemic control and lower the risk of progression of T2DM.[16,19,20] Results from studies have shown that as little as a 1 kg or 1% weight loss can have a substantial benefit for glycemic control, morbidity, and mortality.[16,19,21] Mean 1-year total health care cost was found to be lower for "nonweight gain" patients ($5541) than for patients with weight gain ($7260), with 1 percentage point of weight loss associated with a 3.6% decrease in total health care cost and a 5.8% decrease in T2DM-related cost.[22]

However, treatment-related weight gain is a side effect of some oral antidiabetic agents and insulin. Randomized clinical trials have shown that treatment with insulin, thiazolidinediones (TZDs), and sulfonylureas (SUs) caused weight gain.[23–26] In contrast, treatment with glucagon-like peptide 1 (GLP-1) receptor agonists and metformin result in weight loss.[25–28] The Diabetes Prevention Program (a randomized, double-blind trial of metformin vs. placebo) found that weight loss while on metformin therapy was related to better adherence to therapy, an effect that was durable for at least 10 years of treatment.[28] However, it is unknown whether weight change has an impact on medication adherence among patients with T2DM outside of a clinical trial setting. The objective of this study was to investigate whether adults with T2DM treated in routine clinical practice who lost weight had better medication adherence than those who gained weight.

Methods

The present investigation is an analysis of data from SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes) assessing the relationship between weight loss and adherence to antidiabetic medications. SHIELD is a 5-year, survey-based study conducted to better understand patterns of health status, health behavior, and quality of life of people living with diabetes and those with varying levels of cardiometabolic risk.

SHIELD Survey

SHIELD included an initial screening phase to identify cases of interest in the general adult population (eg, diabetes mellitus), a baseline survey to follow identified cases with a questionnaire about health status, health knowledge and attitudes, and current behaviors and treatments, and annual follow-up surveys for 5 years. A detailed description of the SHIELD methodology was published previously.[29,30]

In brief, the screening survey was mailed in April 2004 to a stratified random sample of 200,000 US households, representative of the US population for geographic residence, household size and income, and age of the head of household,[31] identified by the Taylor Nelson Sofres National Family Opinion panel (Greenwich, Conn). All Taylor Nelson Sofres National Family Opinion surveys were voluntary, and no special incentives were provided. A response rate of 64% (128,000 households with data on 211,097 individuals) was obtained for the screening survey. SHIELD was approved by the Quorum Review Board.

A comprehensive baseline survey was mailed in September through October 2004 to a representative sample of adults (N = 22,001) who were identified in the screening survey as having self-reported type 1 diabetes mellitus or T2DM, no diabetes, or being at risk for diabetes. Each respondent group was balanced to be representative of that segment of the population for age, sex, geographic region, household size, and income for the US population, and then a random sample from each group was selected and sent the baseline survey. A response rate of 72% was obtained for the baseline survey. The 2007 and 2008 annual follow-up surveys had a response rate of 69% and 71%, respectively. Data obtained from the 2008 survey and weight from the 2007 survey were analyzed and reported in this study for respondents with T2DM.

Study measures

Respondents were classified as having T2DM based on their self-report of having been told by a doctor, nurse, or other health care professional that they had T2DM. Weight and height were self-reported at the time of the 2007 and 2008 surveys, and body mass index (BMI) was calculated. Weight change was computed by subtracting the weight reported in the 2007 survey from the weight reported in the 2008 survey. Three weight-loss categories (loss of $>1\%$, $\geq 3.0\%$, and $\geq 5.0\%$) were evaluated to determine whether a small amount of weight loss ($>1\%$) was associated with medication adherence as well as greater weight loss ($\geq 3.0\%$ and $\geq 5.0\%$). One weight gain category ($>1.0\%$) was used because previous studies indicated that any weight gain is detrimental to health.[17–19] Previous studies demonstrated that weight changes of 1% and 5% are important for morbidity and mortality.[16,19,21,32] Overweight was defined as BMI of 25.0 to 29.9 kg/m^2, and obese was defined as BMI ≥ 30 kg/m^2.

The Morisky survey was used to measure patient adherence to medications in 2008. The Morisky survey is a 4-item questionnaire with yes/no responses for (1) ever forget to take the medicine, (2) careless at times about taking the medicine, (3) stop taking medicine sometimes when you feel better, and (4) stop taking medicine sometimes if you feel worse.[33] A no response was scored as 0 and a yes response was 1 point. Scores range from 0 to 4, with higher scores indicating poor adherence. The Morisky scale has been validated and found to be reliable in a variety of medication adherence studies.[10,33–35] A Morisky score was calculated for each antidiabetic medication reported by the respondent in 2008. For respondents receiving ≥ 2 antidiabetic medications, the mean Morisky score was calculated.

Two drug groups were defined based on the weight association for each antidiabetic drug class: (1) drugs associated with weight loss, including GLP-1 receptor agonists and metformin and (2) drugs associated with weight gain, including TZDs, insulin, and SUs. Respondents who received a diabetes treatment regimen with >1 antidiabetic drug that included any weight-gain drug (TZDs, insulin, SUs) were grouped into the weight-gain drug group regardless of other antidiabetic drugs (GLP-1 receptor agonists, metformin, dipeptidyl peptidase-4 [DPP-4] inhibitors) in that treatment regimen. Respondents who received a DPP-4 inhibitors and no other antidiabetic drug (monotherapy) were not included in the analysis of adherence by drug group because DPP-4 inhibitors are weight neutral.[16]

Exercise habits were determined by the survey question that asked respondents to choose "the following statement that best describes your current exercise routine": "I currently exercise regularly," "I currently exercise some, but not regularly," or

"I currently do not exercise." Physical activity level was assessed using the International Physical Activity Questionnaire.[36] The International Physical Activity Questionnaire scores are categorized into 3 levels: (1) low or inactive, (2) moderate activity of at least ≥3 days of vigorous activity of at least 20 minutes per day or ≥5 days of moderate activity or walking of at least 30 minutes per day, and (3) high activity of a minimum of vigorous activity on at least 3 days or 7 days of any combination of walking, moderate or vigorous activities. For diet and eating habits, respondents were asked whether they had or had not followed any diet plans in the past 6 months, including the following: therapeutic lifestyle diet, Mediterranean diet, Atkins diet, South Beach diet, Weight Watchers, vegetarian/vegan diet, other low-fat, high-complex carbohydrate diet, other low-carbohydrate diet, or other low-calorie diet. Respondents were also asked "how many times a week do you usually eat at a fast food restaurant?"

Statistical analysis

The proportion of respondents who lost weight (>1.0%, ≥3.0%, ≥5.0%) or gained weight (>1.0%) from 2007 to 2008 was computed for respondents with T2DM. Respondents who had ±1.0% weight change (weight neutral) were excluded from the analysis, as the association with medication adherence was expected to be negligible. Comparisons between T2DM respondents who lost weight and those who gained weight were made using χ^2 tests for categorical variables and t tests for continuous variables. The power analysis indicated that with an $\alpha = 0.05$, power = 0.80, and $P = 0.50$, the minimum detectable effect size was 0.133 for a sample size of 1400 subjects (>1.0% weight loss), 0.147 for sample size of 1150 (≥3.0% weight loss), and 0.159 for sample size of 980 (≥5.0% weight loss). Linear regression with Morisky score as the dependent variable and age, sex, race, education, income, exercise, diet plan, overweight/obese, weight loss group, and drug group as independent variables were used to test the association with Morisky scores. Statistical significance was set a priori as $P < 0.05$.

Results

Among respondents with T2DM who completed the 2007 and 2008 SHIELD surveys, 746 respondents lost >1.0% in weight, 483 lost ≥3.0%, 310 lost ≥5.0% and 670 respondents gained >1.0% in weight. Each of the weight-loss cohorts was statistically similar to the weight-gain cohort in sex, race, education, household income, household composition, exercise habits, physical activity level, and diet habits (Table I). The weight-loss cohorts were 1.5 to 2.7 years older than the weight-gain cohort ($P < 0.001$), and the weight-loss cohorts had a lower BMI and fewer obese individuals than the weight-gain cohort ($P < 0.001$). With regard to antidiabetic medications, 411 respondents (21.9%) received only weight-lowering drugs (GLP-1 receptor agonist, metformin), and 1449 (77.4%) received weight-gain drugs (13 respondents received DPP-4 monotherapy). Among respondents who lost weight and received weight-lowering antidiabetic drugs, 91% received metformin monotherapy, 1% received GLP-1 receptor agonist monotherapy, and 8% received metformin and GLP-1 receptor agonist combination therapy. For respondents who gained weight and received weight-gain diabetes drugs, 33.5% received monotherapy (TZD, insulin, or SU) and ~50% received metformin or a GLP-1 receptor agonist in combination with TZD, insulin, or SU. More respondents in the weight-loss groups (24%–28%) received antidiabetic medications that were associated with weight loss (metformin and/or GLP-1 receptor agonist) than respondents in the weight-gain group (19%) ($P < 0.01$). Conversely, more respondents in the weight-gain group (81%) received antidiabetic medications that were associated with weight gain (TZDs, insulin, SUs) than respondents in the weight-loss groups (73%–76%).

For each of the 3 weight-loss cohorts, mean Morisky scores were lower, indicating better adherence, than the Morisky scores

Table I
Characteristics of respondents with type 2 diabetes mellitus who lost or gained weight.*

Characteristic	>1.0% Weight Loss (n = 746)	≥3.0% Weight Loss (n = 483)	≥5.0% Weight Loss (n = 310)	>1.0% Weight Gain (n = 670)
Age, y, mean (SD)	64.7 (11.8)	64.8 (12.1)	63.6 (12.3)	62.1 (11.1)†
Women	62.3	64.6	66.5	61.8
White	71.7	71.8	72.9	72.4
Hispanic heritage	7.0	7.7	7.7	5.8
Education, high school degree or less	36.5	37.3	39.2	32.4
Household income, <$30,000	39.5	42.0	44.8	33.7
Single-member household	31.0	33.1	31.9	29.3
Exercise habits				
Currently exercises regularly	24.3	25.0	26.6	23.5
Currently exercises some but not regularly	38.9	37.6	38.0	40.7
Does not currently exercise	36.8	37.4	35.4	35.8
International Physical Activity Questionnaire				
Inactive	63.5	62.7	62.0	66.1
Minimally active	23.4	25.1	23.3	22.0
Highly active	13.1	12.2	14.8	11.9
Followed diet plan	31.2	31.5	32.3	28.5
Eat at fast food restaurant ≥2 times/wk	23.0	21.7	22.9	28.0 †
Body mass index category				
Normal weight (<25.0 kg/m^2)	14.8	17.1	16.6	6.0
Overweight (25.0–29.9 kg/m^2)	24.6	24.4	26.4	22.4
Obese (≥30.0 kg/m^2)	60.6	58.5	57.0	71.5
Mean (SD)	33.2 (8.3)	33.1 (8.7)	33.2 (8.9)	35.6 (8.3)† †
Antidiabetic drug group				
TZD, insulin, and/or SU	72.5	73.8	75.9	80.9
GLP-1 receptor agonist and/or metformin	27.5	26.2	24.1	19.1

GLP-1, glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidinedione.

*Unless indicate otherwise, values shown are percentages.
†$P < 0.05$ for comparison of weight loss (>1.0%) versus weight gain (>1.0%); 1 lb = 0.4536 kg.

Table II
Morisky scores in 2008 for respondents with type 2 diabetes by weight change.

Morisky Score	Weight Loss, %	Weight Gain, %	*P*
	>1.0	**>1.0**	
No.	661	601	
Mean (SD)	0.389 (0.727)	0.473 (0.803)	0.050
	≥3.0	**>1.0**	
No.	426	601	
Mean (SD)	0.365 (0.714)	0.473 (0.803)	0.026
	≥5.0	**>1.0**	
No.	277	601	
Mean (SD)	0.334 (0.721)	0.473 (0.803)	0.014

of the weight-gain cohort (Table II). For the T2DM respondents who lost >1.0% in weight, the mean Morisky score difference trended toward statistical significance ($P = 0.050$), whereas the difference was statistically significant for those who lost greater amounts of weight ($P = 0.026$ for weight loss ≥3.0% and $P = 0.014$ for weight loss ≥5.0%). There was a decrease in Morisky scores as weight loss increased: 0.389 for the >1.0% weight-loss cohort to 0.334 for the ≥5.0% weight-loss cohort.

Morisky scores were lower (better adherence) among T2DM respondents who lost weight and received TZDs, insulin, or SUs compared with T2DM respondents who gained weight and received TZDs, insulin, or SUs (Table III). The difference in Morisky scores among respondents who received TZDs, insulin, or SUs was statistically significant ($P < 0.05$) for each of the 3 weight-loss groups versus the weight-gain group. T2DM respondents who lost weight and received a GLP-1 receptor agonist or metformin had lower Morisky scores (better adherence) than T2DM respondents who gained weight and received a GLP-1 receptor agonist or metformin, but the difference was not significant ($P > 0.10$).

A linear regression model adjusting for age, sex, race, education, income, exercise, diet plan, overweight/obese, and drug group found that Morisky scores were negatively associated (better adherence) with receiving weight-loss antidiabetic drugs in the respondents with >1% weight loss ($P = 0.002$) and respondents with ≥3.0% weight loss ($P = 0.004$) but not among respondents with ≥5% weight loss ($P = 0.08$) (Table IV). Weight loss of ≥3% and ≥5% compared with weight gain was significantly associated with lower Morisky scores after adjustment.

Discussion

In this population-based study, each weight-loss cohort had better antidiabetic medication adherence compared with the weight-gain cohort. Even a small weight loss of >1% was associated with a positive impact on medication adherence, and the association with medication adherence was greater with greater weight loss. Significantly fewer respondents who lost weight had received antidiabetic medications that caused weight gain (TZDs, insulin, SUs) compared with respondents who gained weight, and adherence was better (lower Morisky scores) among respondents who lost weight and received antidiabetic drugs that caused weight gain (TZDs, insulin, SUs) compared with respondents who gained weight and received TZDs, insulin, or SUs. Other factors that were assessed did not explain the association between weight loss and better medication adherence, as the weight-loss cohorts were similar to the weight-gain cohort for demographics, exercise, physical activity, and dieting and eating habits.

There appeared to be a "dose response" to weight loss and better medication adherence. Small amounts of weight loss (>1%) were associated with better medication adherence, and ≥5% loss of weight had a stronger association with improved medication adherence. The >1% weight-loss cohort had, on average, a 17.8% better adherence score than the weight-gain cohort, whereas the ≥3% and ≥5% weight-loss cohorts had 22.8% and 29.4% better adherence scores than the weight-gain cohort, respectively. Additionally, medication adherence was better (lower scores) as weight loss increased among those who received antidiabetic drugs that cause weight gain and among those who received only metformin and/or a GLP-1receptor agonist. These findings provide further evidence of the importance of managing weight in the overall disease management of diabetes. As previous studies showed that better medication adherence improves glycemic control,[3,8–10] it would be expected that the T2DM respondents in the present study who lost weight and had better medication adherence would also have better glycemic control. Using the 0.34% reduction in HbA_{1c} for every 25% increase in medication adherence from the Rhee et al study,[9] it is possible that the ≥3% and ≥5% weight-loss cohorts could be expected to have ~0.34% lower HbA_{1c} than the weight-gain cohort. The SHIELD did not collect HbA_{1c} levels from the respondents, so the actual glycemic control could not be assessed. The respondents who lost weight and had better medication adherence would also be expected to have lower rates of hospitalization and lower health care costs based on the findings of other studies.[11–13]

Other factors in addition to weight change for certain antidiabetic drugs may affect medication adherence. Certain antidiabetic drugs are associated with a higher rate of hypoglycemia, and GLP-1 drugs and insulin are injectables, which may adversely affect medication adherence. The side effects of antidiabetic drugs and the severity of diabetes were not captured in the SHIELD so they could not be evaluated in the present study.

The findings of the present study are similar to the findings in the Diabetes Prevention Program, which also showed better adherence to therapy among patients who lost weight.[28] In the long-term follow-up analysis of the Diabetes Prevention Program,

Table III
Morisky scores in 2008 for respondents with type 2 diabetes by weight change and diabetes drug group.

Drug Group	>1.0% Weight Loss	≥3.0% Weight Loss	≥5.0% Weight Loss	>1.0% Weight Gain	P for Weight Loss Versus Weight Gain
Weight-gain drugs: TZD, insulin, and/or SU					
No.	470	307	206	483	
Morisky score, mean (SD)	0.338 (0.673)	0.311 (0.646)	0.303 (0.660)	0.432 (0.775)	0.048 for >1.0% loss, 0.023 for ≥3.0% loss, 0.038 for ≥5.0% loss
Weight-loss drugs: GLP-1 receptor agonist and/or metformin					
No.	185	115	68	114	
Morisky score, mean (SD)	0.530 (0.841)	0.522 (0.862)	0.441 (0.887)	0.658 (0.901)	0.21 for >1.0% loss, 0.24 for ≥3.0% loss, 0.12 for ≥5.0% loss

GLP-1, glucagon-like peptide-1; SU, sulfonylurea; TZD, thiazolidinedione.

Table IV
Linear regression coefficients for Morisky score adjusted for demographic and lifestyle characteristics.

	Weight loss > 1.0%		Weight loss ≥ 3.0%		Weight loss ≥ 5.0%	
	β Coefficient	*P*	β Coefficient	*P*	β Coefficient	*P*
Weight-loss drug vs. weight-gain drug	−0.167	0.002	−0.172	0.004	−0.118	0.081
Age (continuous)	−0.017	< 0.0001	−0.018	< 0.0001	−0.019	< 0.0001
Male vs. female	0.006	0.90	−0.020	0.71	−0.015	0.80
Black vs. white	0.160	0.005	0.150	0.017	0.199	0.003
Other race vs. white	0.193	0.058	0.276	0.014	0.215	0.097
College or graduate courses vs. high school or less	0.051	0.32	0.146	0.009	0.135	0.029
Income, $						
35,000–49,000 vs. < 35,000	0.045	0.46	0.011	0.87	−0.007	0.92
50,000–74,000	−0.020	0.77	−0.047	0.51	−0.030	0.71
≥ 75,000	−0.087	0.20	−0.160	0.030	−0.219	0.008
Exercise regularly (yes/no)	0.105	0.033	0.178	0.001	0.186	0.002
Diet plan in past 6 mo (yes/no)	0.103	0.074	0.117	0.064	0.145	0.038
Tried to lose weight (yes/no)	−0.063	0.22	−0.063	0.267	−0.067	0.28
Overweight vs. normal weight	0.049	0.58	0.021	0.83	0.054	0.63
Obese vs. normal weight	0.071	0.40	0.005	0.96	0.022	0.84
Lost vs. gained weight	0.032	0.16	0.051	0.049	0.067	0.027

patients taking metformin had reduced weight compared with those receiving placebo, and the magnitude of weight loss was directly related to continuing medication adherence.[28] Similar to these findings from the Diabetes Prevention Program, the present study found that adherence was better among respondents who lost weight and received metformin and/or a GLP-1 receptor agonist compared with respondents who gained weight and received metformin and/or a GLP-1 receptor agonist.

Weight change in the present study was similar to that in other studies. A retrospective study of adults with T2DM from a health maintenance organization by Yu et al[22] found that 48.9% of patients experienced weight gain (minimum of 1 pound), and the present study found that 47.3% of study population had > 1% weight gain. Also, Yu et al[22] found that the weight-gain group had significantly higher use of TZDs than the group without weight gain, a finding similar to that in the present study.

The present study used a large, population-based sample of T2DM respondents to assess the association of weight change on medication adherence. There are limitations to the study that should be considered. Information about glycemic control (HbA_{1c}) was not collected in the SHIELD survey, so the impact of improved adherence with weight loss on glycemic control could not be investigated. The determination of T2DM and weight was made based on self-report rather than on clinical or laboratory measures. However, this determination was made consistently for all respondent groups evaluated in this study, so it should not have affected the comparison across groups. Household panels, like the SHIELD, tend to underrepresent the very wealthy and very poor segments of the population and do not include military or institutionalized individuals. These limitations are true for most random sampling and clinically based methodologies. Self-selection bias may be present because respondents were those who could read and comprehend the survey.

Conclusions

Adults with T2DM and weight loss had significantly better medication adherence and were less likely to be on treatment regimens that increase weight than adults with T2DM and weight gain. Based on current diabetes treatment patterns seen in this study, a majority of patients may receive treatment regimens that increase weight. Therefore, consideration of the weight change characteristics of an antidiabetic agent is important when managing patients with T2DM, especially those with obesity. Communicating the benefits of at least 1% reduction in weight on medication adherence, glycemic control, and reduced morbidity and mortality to patients may be an effective approach to diabetes management.

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Conflicts of Interest

Drs. Grandy and Hardy are employees and stockholders of AstraZeneca LP. Dr. Fox received research funds from AstraZeneca LP.

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