MAYO CLINIC

Antidiabetic Effects of the Senolytic Agent Dasatinib

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Abstract

Objective: To evaluate the antidiabetic effects of the senolytic agent dasatinib in older patients with type 2 diabetes mellitus.

Methods: This retrospective cohort study included enterprise-wide Mayo Clinic patients using Informatics for Integrating Biology at the Bedside from January 1994 through December 2019. The antidiabetic outcomes (change in hemoglobin A_{1c} value, serum glucose concentration, and diabetic medications) after 1 year of a strongly senolytic tyrosine kinase inhibitor, dasatinib (n=16), was compared with a weakly senolytic tyrosine kinase inhibitor, imatinib (n=32).

Results: Relative to imatinib, patients treated with dasatinib had a mean reduction of 43.7 mg/dL (P=.005) in serum glucose concentration (to convert glucose values to mmol/L, multiply by 0.0555) and required 28.8 fewer total daily insulin units (P=.08) in the setting of a 4.8-kg relative weight loss (5.3% of total body weight; P=.045). Linear regression analysis suggests that the relative difference in weight accounts for 8.4 mg/dL of the 43.7 mg/dL blood glucose value decrease, or 19.2%. Relative to imatinib, patients treated with dasatinib had a mean 0.80 absolute point (P=.05) reduction in hemoglobin A_{1c} and required 18.2 fewer total daily insulin units (P=.16) in the setting of a 5.9-kg relative weight loss (6.3% of total body weight; P=.06).

Conclusion: Dasatinib may have antidiabetic effects comparable to contemporary diabetic treatments and may be considered for use as a novel diabetic therapy. Future studies are needed to determine whether these results are translatable to patients with type 2 diabetes mellitus without underlying malignant diseases and to determine whether the antidiabetic effects of dasatinib are due to its senolytic properties.

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Type 2 diabetes mellitus (T2DM), affecting an estimated 31 and 425 million people in the United States and worldwide, respectively,[1] entails significant morbidity and mortality. The prevalence of T2DM increases with aging, affecting approximately 18 million Americans older than 65 years.[2] Despite improved understanding of the pathophysiologic process of T2DM, current oral pharmacologic therapies are noncurative and limited in efficacy.

Tyrosine kinase inhibitors (TKIs) are used for the treatment of select malignant neoplasms. Imatinib was the first TKI approved for Philadelphia chromosome—positive chronic myelogenous leukemia in 2001 and was soon followed by other TKIs, such as dasatinib in 2006. Sporadic case reports suggested that TKIs, primarily imatinib, may improve glycemic control or even result in complete remission of T2DM.[3-8] A subsequent retrospective cohort study of patients with (n=17) and without (n=61) T2DM found that treatment with various TKIs (sunitinib, sorafenib, dasatinib, and imatinib) was associated with lower serum glucose levels. This finding was limited by a small T2DM cohort, heterogeneous malignant neoplasms, and possible confounding by progression of the malignant disease and weight changes.[9] Currently, experts recommend

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close monitoring of glucose level on initiation of TKIs because of the potential concern for hypoglycemia.[10] However, other studies examining this issue have been inconsistent.[11,12] The literature is limited by retrospective observational studies with small number of diabetic patients (<10) and potential confounding by malignant disease and alterations in weight.

Whereas TKIs have been suggested as a novel therapy for T2DM, the mechanism of action to reduce hyperglycemia is unclear owing to numerous off-target effects. However, there is a growing body of evidence to suggest that cellular senescence is a cause and consequence of many age-related diseases, including T2DM.[13] In preclinical animal models, reducing senescent cell burden through treatment with senolytic drugs, such as the combination of dasatinib and quercetin, has been reported to improve glucose tolerance and to enhance insulin sensitivity.[14]

Further studies are required to determine whether there is an antidiabetic effect of TKIs in humans with T2DM and, if so, to determine whether this effect is mediated by reducing senescent cell burden. The objective of this retrospective cohort study was to evaluate the antidiabetic effect of the strongly senolytic TKI dasatinib compared with the weakly senolytic agent imatinib.[15]

METHODS

Study Design and Participants
This study was a retrospective cohort design. The cohort was identified using Mayo Clinic's Informatics for Integrating Biology at the Bedside, an informatics framework that organizes and transforms patients' clinic data into a research database. As interrogated, Mayo Clinic's Informatics for Integrating Biology at the Bedside database included patients from campuses in Arizona (1999-2020), Florida (2003-2020), Rochester (1994-2020), and the Mayo Clinic Health System in Minnesota (2006-2020). Inclusion criteria were continuous use of dasatinib or imatinib for at least 12 consecutive months, age older than 18 years, and T2DM diagnosed before the initiation of dasatinib or imatinib.

Exclusion criteria were a TKI indication of hypereosinophilia syndrome (treated with concurrent glucocorticoids) for both groups and the use of any prior TKI for the imatinib group. Because dasatinib is typically used as a second-line agent, excluding patients with prior TKI use was not always possible.
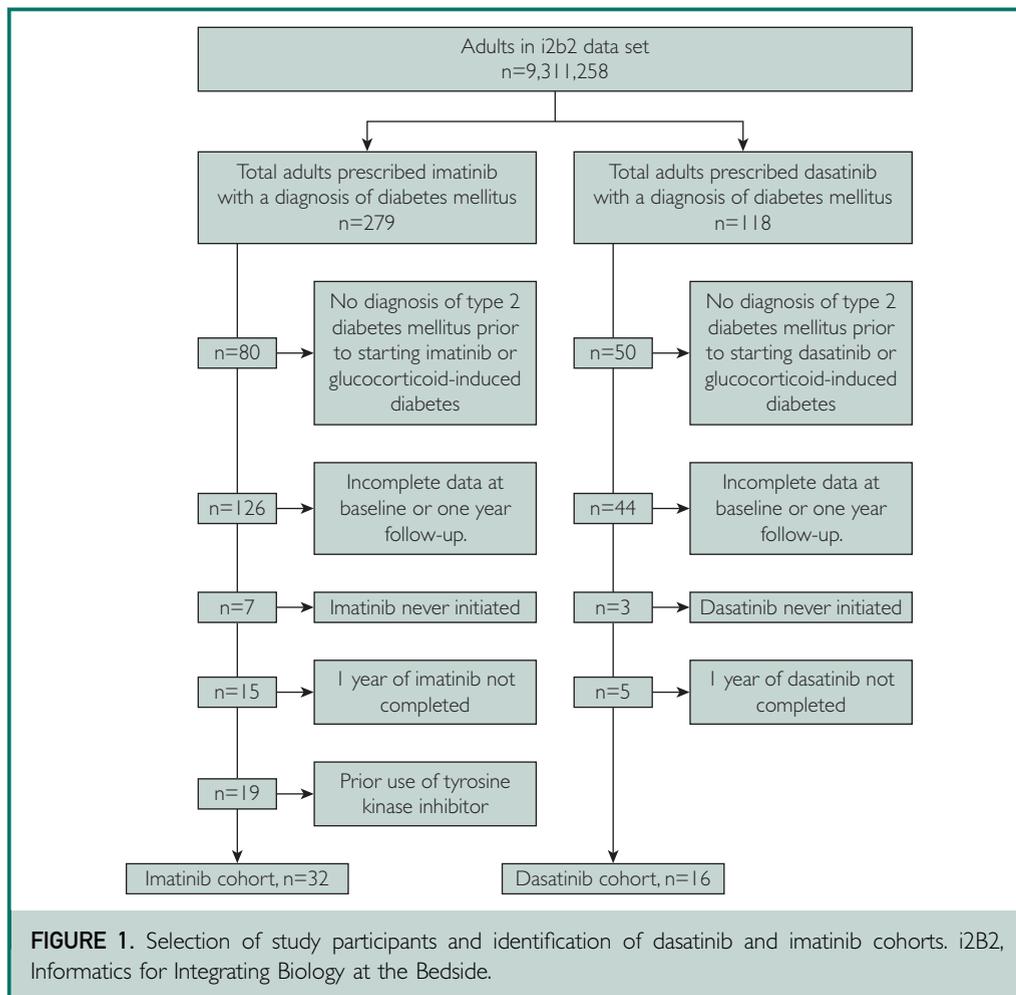
Data were obtained through medical record chart review. Hemoglobin A_{1c} level, serum blood glucose concentration, weight, and information about diabetic medications were collected at the time of initiation of dasatinib or imatinib and again 12 months later. Individuals were included only if they had values recorded less than 3 months before the initiation of the TKI. Fasting outpatient serum glucose values were obtained, and if not specified, the lowest outpatient morning glucose value was recorded. Total daily insulin dose was calculated by adding fixed long- and short-acting insulin units (sliding scale or carbohydrate correction insulin doses were not included).

Statistical Analyses
A 2-sided unpaired Student t-test was used to compare differences in continuous variables and Fisher exact test to compare differences in categorical variables between the dasatinib and imatinib groups. The association between the change in weight loss and the change in hemoglobin A_{1c} level or glucose concentration was evaluated by group (dasatinib or imatinib) using a simple linear regression model and was compared between groups using the model with weight loss, group, and their interaction for hemoglobin A_{1c} or glucose. A significant interaction in the model implies differential associations between the dasatinib and imatinib groups. A P value of less than .05 was considered statically significant. All the statistical analyses were performed in Microsoft Excel 2010 and R version 3.6.1 (R Foundation for Statistical Computing).

Compliance with Ethical Standards
The Mayo Clinic Institutional Review Board approved this study. This study was exempted from the need to obtain informed consent.

FIGURE 1. Selection of study participants and identification of dasatinib and imatinib cohorts. i2B2, Informatics for Integrating Biology at the Bedside.

RESULTS

Characteristics of Study Participants

A total of 9,311,258 individuals were screened for use of either dasatinib or imatinib. There were 279 and 118 individuals included in the imatinib and dasatinib groups, respectively (Figure 1). A total of 247 individuals were removed from the imatinib group because of failure to meet inclusion and exclusion criteria, resulting in a cohort of 32 individuals. Baseline and 1-year data were complete in 26 of 32 and 22 of 32 individuals for serum glucose concentration and hemoglobin A_{1c} level, respectively. A total of 102 individuals were removed from the dasatinib group after application of inclusion and exclusion criteria, resulting in a cohort of 16 individuals. In the dasatinib group, baseline and 1-year data were complete in 12 of 16 and 13 of 16 individuals for serum glucose concentration and hemoglobin A_{1c} level, respectively.

Tables 1 and 2 provide baseline characteristics of the study participants with respect to changes in serum glucose concentration and hemoglobin A_{1c} level, respectively. Baseline parameters, including mean age at diagnosis of malignant disease, sex, race, type of malignant disease, prior use of TKI, serum glucose value, insulin dependency, total daily insulin requirement, oral antihyperglycemic agents, and weight, were evaluated between the dasatinib and imatinib groups. In comparing serum glucose values, there were no statistically significant differences between the groups other than prior TKI use ($P=.007$). In comparing

	Dasatinib	Imatinib	P value[d]
No.	12	26	
Male	7 (58)	17 (65)	.728
Race, White	10 (83)	24 (92)	.577
Malignant disease			
CML	9 (75)	13 (50)	.178
ALL	2 (17)	1 (4)	.230
GIST	1 (8)	11 (42)	.060
Melanoma	0	1 (4)	>.99
Age at diagnosis (y)	61.7±10.9	64.0±11.0	.304
TKI before dasatinib or imatinib	4/12 (33)	0	**.007**
Baseline glucose (mg/dL)	145±48	132±39	.414
On insulin	4 (33)	7 (25)	.714
Average total daily units	71±47	67±52	.907
On oral agents	10 (83)	19 (73)	.689
No. of agents	1.2±0.8	1.0±0.8	.568
Baseline weight (kg)	98.5±23.5	95.6±23.0	.728

[a]ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

[b]To convert glucose values to mmol/L, multiply by 0.0555.

[c]Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± standard deviation.

[d]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

hemoglobin A_{1c} values, there were no statistically significant differences between the groups other than prior TKI use ($P=.01$) and gastrointestinal stromal tumor diagnoses ($P=.02$).

Change in Glycemic Control after 1 Year of TKI Therapy

Table 3 displays the change in serum glucose values after 1 year of either dasatinib or imatinib. Relative to imatinib, the dasatinib group had a decrease of 43.7 mg/dL ($P=.005$) in serum glucose concentration (to convert glucose values to mmol/L, multiply by 0.0555). Total daily insulin requirements decreased by 28.8 units ($P=.08$), whereas use of other antihyperglycemic agents was unchanged (decrease by 0.04; $P=.66$). Relative body weight decreased by 4.8 kg ($P=.045$), equivalent to a change of -5.3% ($P=.03$). Of note, 2 of 4 insulin-dependent patients in the dasatinib group did not require any insulin (weight decrease of 1.5 and

2.5 kg) compared with 1 of 9 insulin-dependent patients (weight decrease of 18 kg) in the imatinib group.

Table 4 displays the change in hemoglobin A_{1c} values after 1 year of either dasatinib or imatinib. Relative to imatinib, the dasatinib group had an absolute decrease in hemoglobin A_{1c} value of 0.80% ($P=.05$). Total daily insulin requirements decreased by 18.2 units ($P=.16$), whereas use of other antihyperglycemic agents was unchanged ($P=.93$). Relative body weight decreased by 5.9 kg ($P=.06$), equivalent to a change of -6.3% ($P=.04$).

A sensitivity analysis that excluded 5 patients with prior TKI use in the dasatinib group is shown in Tables 5 and 6. This found that relative to treatment with imatinib, patients treated with dasatinib had a larger magnitude of hypoglycemic effect for both serum glucose and hemoglobin A_{1c} values as well as a significant reduction in body weight.

A simple linear regression (Figure 2) was used to evaluate the association between change in body weight and changes in either serum glucose concentration or hemoglobin A_{1c} level for the dasatinib and imatinib groups separately. The mean change in glucose concentration was 0.42 mg/dL (95% CI, -5.85 to 6.69) per kilogram decrease in weight in the dasatinib group but 2.44 mg/dL (95% CI, 0.75 to 4.13) per kilogram in the imatinib group. The between-group difference did not reach statistical significance ($P=.49$). The hemoglobin A_{1c} decrease was 0.10% (95% CI, 0.04 to 0.17) per kilogram weight loss in the dasatinib group, which was similar to the value of 0.08% (95% CI, 0.04 to 0.13) in the imatinib group ($P=.63$).

DISCUSSION

In this study, we report that dasatinib, compared with imatinib, lowers serum glucose values in patients with preexisting T2DM by almost 45 mg/dL, with perhaps a reduction of total daily insulin requirements (-28.2 daily units; $P=.08$) and absolute reduction of hemoglobin A_{1c} values (-0.80%; $P=.05$). This hemoglobin A_{1c} decrease is quantitatively comparable to that which occurs with the use

TABLE 2. Baseline Characteristics of Dasatinib vs Imatinib: Hemoglobin A$_{1c}$ Values[a,b]

	Dasatinib	Imatinib	P value[c]
No.	13	22	
Male	9 (69)	11 (50)	.31
Race, White	11 (85)	20 (91)	.18
Malignant disease			
CML	11 (85)	13 (59)	.15
ALL	2 (15)	1 (5)	.54
GIST	0	8 (36)	**.02**
Melanoma	0	0	>.99
Age at diagnosis (y)	62.6±11.2	66.6±10.3	.31
TKI before dasatinib or imatinib	4/13 (31)	0	**.01**
Baseline hemoglobin A$_{1c}$ (%)	6.9±0.8	6.5±0.8	.24
On insulin	6 (46)	7 (32)	.48
Average total daily units	69±51	56±49	.65
On oral agents	9 (69)	19 (86)	.38
No. of agents	1.1±0.9	1.2±0.7	.71
Baseline weight (kg)	102.8±19.6	95.9±24.1	.36

[a]ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

[b]Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± standard deviation.

[c]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

of hypoglycemic agents commonly used as first-line agents, such as metformin and sulfonylureas, which typically lower hemoglobin A$_{1c}$ values by 1% to 2%; thiazolidinediones, by 0.5% to 1.4%; glucagon-like peptide 1 receptor agonists, by 0.5% to 1.5%; sodium-glucose co-transporter 2 receptor antagonists, by 0.5% to 0.7%; and dipeptidyl peptidase 4 inhibitors, by 0.5% to 0.8%.[16] Imatinib was chosen to be the control group for the following reasons: like dasatinib, it is a TKI; it is used in the treatment of similar malignant neoplasms; and compared with dasatinib, it represents the less efficacious end of the spectrum of senolytic agents.

The improved glycemic control in patients treated with dasatinib compared with imatinib was in the context of a relative weight loss of −4.80 kg (P=.045) after 1 year, or −5.3% of total body weight. There

TABLE 3. Serum Glucose and Other Glycemic Indices After 1 Year of TKI Therapy[a,b,c]

	Dasatinib	Imatinib	Difference	P value[d]
No.	12	26		
Serum glucose (mg/dL)	−31.4±34.2	12.3±43.6	−43.7	**.005**
Total daily insulin units	−23.5±22.2	5.3±19.2	−28.8	.08
Other antihyperglycemic medications	0.0±0.0	0.04±0.45	−0.04	.66
Weight (kg)	−1.62±4.89	3.18±9.30	4.80	**.045**
Body mass (%)	−1.7±2.3	3.6±8.9	5.3	**.03**

[a]TKI, tyrosine kinase inhibitor.

[b]To convert glucose values to mmol/L, multiply by 0.0555.

[c]Values are presented as mean ± standard deviation.

[d]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

TABLE 4. Hemoglobin A_{1c} and Other Glycemic Indices After 1 Year of TKI Therapy[a,b]

	Dasatinib	Imatinib	Difference	P value[c]
No.	13	22		
Hemoglobin A_{1c} (%)	−0.74±1.06	0.06±1.25	−0.80	**.05**
Total daily insulin units	−18.8±21.9	−0.6±15.3	−18.2	.16
Other antihyperglycemic medications	−0.1±0.3	−0.1±0.6	0.0	.93
Weight (kg)	−3.0±7.6	2.8±10.1	5.9	.06
Body mass (%)	−3.1±3.06	3.2±9.6	6.3	**.04**

[a]TKI, tyrosine kinase inhibitor.
[b]Values are presented as mean ± standard deviation.
[c]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

was no statistically significant difference in relative weight change seen for the reduction in hemoglobin A_{1c}. Weight loss is key to improving glycemic control, and intentional weight loss of 10% has been reported to reduce hemoglobin A_{1c} by 0.81% (or about 23 mg/dL) in patients with T2DM.[17] Our linear regression analysis (Figure 2) comparing change in glucose concentration with change in weight for the dasatinib and imatinib groups suggests that the relative difference in weight accounts for only 8.4 mg/dL of the 43.7 mg/dL blood glucose value decrease, or 19.2%.

The magnitude of improvement in glycemic control in response to treatment with TKIs is not well established in the current literature. A previous retrospective cohort study found that dasatinib treatment lowers mean serum glucose values by 52 mg/dL regardless of T2DM status,[9] whereas prior case reports have found improvements including remission of preexisting T2DM.[5,6,8,17,18] Our finding of an absolute improvement of serum glucose values by 31.4 mg/dL, including 2 of 4 patients who no longer required insulin within 12 months of dasatinib initiation, is consistent with prior literature on the antidiabetic properties of dasatinib. Retrospective cohort studies are conflicting about the impact of imatinib on glycemic control, with some reporting a modest improvement in serum glucose concentration (9 mg/dL)[9] and other studies reporting no improvement.[11,12,19] These observations are consistent with our finding of an absolute increase in serum glucose concentration of 12.3 mg/dL in patients treated with imatinib. The few cohort studies that examined the impact of

TABLE 5. Serum Glucose and Other Glycemic Indices After 1 Year of TKI Therapy, Excluding Prior TKI Therapy[a,b,c]

	Dasatinib	Imatinib	Difference	P value[d]
No.	8	26		
Serum glucose (mg/dL)	−33.6±30.1	12.3±43.6	−45.9	**.007**
Total daily insulin units	−33±30.0	5.3±19.2	−38.3	.30
Other antihyperglycemic medications	0±0.0	0.04±0.45	−0.04	.66
Weight (kg)	−2.8±4.71	3.2±9.30	6.0	**.02**
Body mass (%)	−2.7±3.8	3.6±8.9	6.3	**.02**

[a]TKI, tyrosine kinase inhibitor.
[b]To convert glucose values to mmol/L, multiply by 0.0555.
[c]Values are presented as mean ± standard deviation.
[d]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

TABLE 6. Hemoglobin A_{1c} and Other Glycemic Indices After 1 Year of TKI Therapy, Excluding Prior TKI Therapy[a,b]

	Dasatinib	Imatinib	Difference	P value[c]
No.	9	22		
Hemoglobin A_{1c} (%)	−1.08±1.09	0.06±1.25	−1.14	**.02**
Total daily insulin units	−22.0±28.4	−0.6±15.3	−21.4	.32
Other antihyperglycemic medications	−0.1±0.3	−0.1±0.5	0.0	.91
Weight (kg)	−5.0±8.1	2.8±10.1	7.9	**.04**
Body mass (%)	−5.0±0.9	3.2±9.6	8.3	**.03**

[a]TKI, tyrosine kinase inhibitor.

[b]Values are presented as mean ± standard deviation.

[c]P values were obtained using a 2-tailed 2-sample t-test assuming unequal variances for continuous variables or Fisher exact test for categorical variables. Boldface P values represent statistical significance.

TKI treatment on glycemic control included heterogeneous malignant neoplasms, had small populations of patients with and without T2DM, observed patients for a variable duration, and did not control for longitudinal weight changes. Our study used the largest cohort of T2DM patients receiving

FIGURE 2. Association between change in serum glucose concentration or hemoglobin A_{1c} level and change in weight in the dasatinib and imatinib cohorts.

TKI treatment and controlled for weight change.

There are several limitations to our study. First, included patients had heterogeneous malignant disease indications at baseline for the selection of 2 TKI therapies, and underlying disease aggressiveness was not directly measured. This was mitigated by our requirement for 1 year of continuous TKI therapy, a requirement that excluded patients who died within 1 year of TKI initiation or in whom disease progression developed that would have prompted a change in TKI therapy. Second, 5 of 16 individuals in the dasatinib group received prior TKI therapy. Given prior reports of a class antidiabetic effect of TKIs,[20] this may have underestimated the magnitude of a pure dasatinib effect and therefore increases the robustness of our findings regarding the potential antidiabetic effects of dasatinib. This is supported in our sensitivity analysis, which excluded 5 patients with prior TKI use. Third, nonpharmacologic interventions to improve glycemic control, such as exercise and dietary changes, could not be directly measured. Instead, weight was considered a reasonable proxy. Fourth, serum glucose and hemoglobin A_{1c} levels were sometimes lacking, creating smaller subcohorts. Finally, this study was of a single health care system, which limits external generalizability.

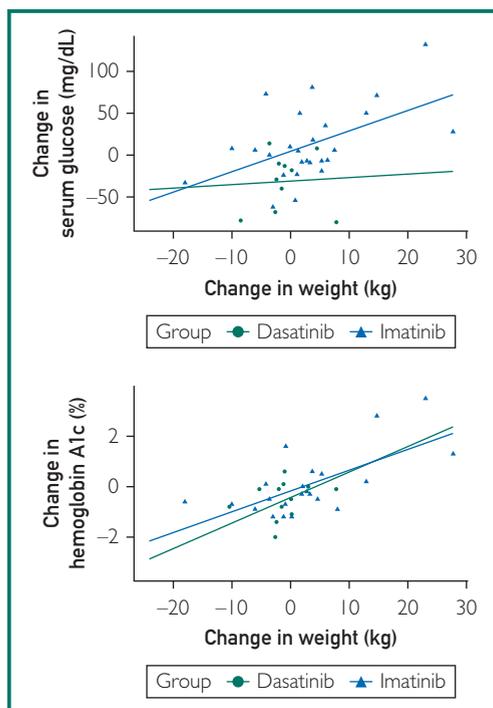Potential confounders included changes in oral antihyperglycemic agent and

management of malignant disease. Changes in oral antihyperglycemic medications were negligible. Only 1 of 16 patients treated with dasatinib had a change (from 1 to 0 oral medications). Of 32 patients treated with imatinib, 7 had a change (3 patients discontinued medications, 1 of whom discontinued 2 medications; 4 patients started new medication, with a net change of 0). Another potential confounder is management of malignant disease that could affect weight, especially edema, which is a known adverse reaction to TKIs (particularly dasatinib). In our cohort, we do not suspect that it played a major role because clinically significant edema is an indication for a change in therapy.

The potential mechanism behind the antidiabetic effects of TKIs remains an area of continuing investigation. Potential mechanisms based on in vivo and in vitro studies suggest the following: Abelson tyrosine kinase (c-Abl) inhibition increases beta cell survival; platelet-derived growth factor receptor and epidermal growth factor receptor inhibition improves insulin sensitivity; and inhibition of vascular endothelial growth factor receptor 2 reduces insulitis.[20] Antidiabetic effects from multiple TKIs may be a result of influences on 1 or more of these various targets.

Apart from these potential roles for TKIs in modulating glycemia, increasing evidence from animal models suggests that cellular senescence may be a key driver of T2DM. Excessive calorie intake in mice to induce T2DM resulted in the generation of increased senescence factors, including upregulation of p53 and insulin resistance.[21] Likewise, hyperglycemia itself was found to cause cellular senescence in the renal tubules in a type 1 diabetes mellitus mouse model.[22] Furthermore, mice with T2DM that were treated with senolytic agents (dasatinib and quercetin) had reduced cellular senescence markers and improved glucose tolerance in addition to enhanced insulin sensitivity.[14] These findings suggest that the antidiabetic effects seen with certain TKIs may be due to their senolytic properties. Indeed, this would also explain why the strong senolytic agent dasatinib would produce greater glycemic control compared with the much weaker senolytic agent imatinib.[15] In addition, it also suggests that the combination of 2 agents with senolytic activity, dasatinib and quercetin, might have even greater antidiabetic effects in humans with T2DM than treatment with dasatinib alone. If determined to be true, this raises the intriguing possibility that senolytic treatment either alone or in combination might need to be given only intermittently, akin to a "hit and run" approach, because repopulation of senescent cells after clearance in response to senolytic exposure is expected to occur during the order of weeks.[23]

Current senolytics such as dasatinib and quercetin are limited by cost and adverse effect profile; safer and improved drugs targeting senescence are needed. The natural flavonoid fisetin has been reported to have similar senolytic properties to dasatinib and quercetin in progeroid and aged mice.[24] If the glycemic benefit of dasatinib is indeed through senescence clearance, fisetin is an attractive alternative senolytic in future clinical trials.

CONCLUSION

This retrospective cohort study found that dasatinib used for the treatment of malignant disease may have an antidiabetic effect comparable to or perhaps even greater than that of contemporary antidiabetic medications in patients with preexisting T2DM. Our findings suggest that dasatinib or related senolytic drugs may become novel diabetic therapies. Future studies are needed to determine whether these findings can be translated to patients with T2DM but without underlying malignant disease. In addition, further investigation is also needed to determine whether the antidiabetic effect of dasatinib is due primarily to its senolytic properties. If so, the effectiveness of combining senolytic drugs, such as dasatinib and quercetin, for the treatment of T2DM could be greater than that of treatment with dasatinib alone.

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