Published in final edited form as:
Diabetes Care. 2008 March ; 31(3): . doi:10.2337/dc07-1934.

Clinical Predictors of Disease Progression and Medication Initiation in Untreated Patients with Type 2 Diabetes and A1C Less Than 7%

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Abstract

Objective—Many patients with early diabetes remain untreated. Our objectives were to identify clinical predictors of *1*) worsening glycemic control and *2*) medical treatment initiation in response to worsening glycemic control among patients with type 2 diabetes.

Research Design and Methods—We identified 5,804 type 2 diabetic patients seen at least twice between June 2005 and June 2006 within our 12-clinic primary care network. We examined predictors of diabetes progression (A1C ≥7% or initiation of hypoglycemic agent) over a 1-year follow-up period in 705 patients who had A1C <7% and were not on glucose-lowering medications at baseline. In the 200 patients in this group who progressed, we examined predictors of medical therapy initiation.

Results—In multivariate analyses, baseline A1C ($P < 0.0001$), younger age ($P = 0.04$), and weight gain ($P = 0.03$) were independent predictors of progression after adjusting for race, sex, and baseline HDL levels. Each decade of increasing age reduced the risk of progression by 15%. Each 1-lb increase in weight was associated with a 2% increased odds of progression. Likelihood of medication initiation among progressors decreased by 40% ($P = 0.02$) with every decade of age and decreased by 2.3% ($P = 0.02$) with each 1-mg/dl decrease in LDL level from baseline after adjusting for race, sex, and weight change.

Conclusions—Among untreated primary care patients with type 2 diabetes and A1C < 7%, younger patients and those with weight gain were more likely to have diabetes progression and should be the focus of aggressive diabetes management.

Evidence from the UK Prospective Diabetes Study (UKPDS) suggests that early medical treatment may slow progression of type 2 diabetes (1,2). However, in current practice a significant proportion of patients with type 2 diabetes are initially managed without medications (3). Based in part on data demonstrating a reduction in long-term complications with glycemic control maintained as close to the nondiabetic range as possible (4–6), the American Diabetes Association has recently published management guidelines that advocate simultaneous lifestyle changes and metformin as initial therapy for all patients with type 2 diabetes (7).

Although type 2 diabetes is a progressive disease, patients in the early stages of diabetes may advance at different rates. While prior studies have identified factors predicting glycemic control among patients with type 2 diabetes on therapy (8– 11), we have not found

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studies that have examined predictors of disease progression in patients with A1C <7% and not on medication therapy. Moreover, no studies have addressed this question in the "usual care" outpatient setting, where most patients first diagnosed with type 2 diabetes are initially managed. Furthermore, no recent studies have examined the factors associated with early initiation of glucose-lowering medications.

Identifying a subgroup of patients with type 2 diabetes at low risk of progression and who may be managed without medications (and their attendant costs and side-effects) will help guide the cost-effective management of the diabetes epidemic. We therefore investigated the clinical course over 1 year of follow-up for all patients with type 2 diabetes in a 12-practice primary care network who had A1C <7% and were not on medical therapy at baseline to identify *1*) predictors of type 2 diabetes progression (defined as A1C ≥7% or treatment initiation) and *2*) predictors of medication initiation versus remaining on diet/lifestyle-only therapy among the subset of type 2 diabetic patients who did progress.

Research Design and Methods

Study subjects were identified from the population of patients with type 2 diabetes receiving regular primary care in 12 outpatient practices in eastern Massachusetts. This patient registry has been described in detail (12) and has been used in a wide range of prior studies investigating diabetes care (12– 14). In brief, the study practices include three hospital-affiliated academic practices, four community health centers, and five private offices that serve a wide range of communities and a diverse patient population. Patients were defined as having type 2 diabetes using a previously validated algorithm that included Electronic Medical Record problem lists, diabetes-specific medications, and/or A1C results >7%. This algorithm has 98% sensitivity and 98% specificity compared with the gold standard of manual chart review by a trained research nurse. The registry database includes complete electronic medical record data of patients with type 2 diabetes between June 2004 and June 2006 and two complete cross-sectional medication lists, one from 30 June 2005 and the other from 30 June 2006. The database also includes demographic information (age, sex, primary care physician [PCP], insurance type, estimated household income based on zip code, and race); clinical data including any history of coronary artery disease, hypertension, smoking, dyslipidemia, and obesity, systolic and diastolic blood pressure, weight, and height; and laboratory data including A1C, microalbuminuria levels, lipid profiles, and liver and kidney function tests.

Patients included in the study were at least 18 years of age and had a designated PCP in one of the 12 primary care clinics with at least one documented visit with their PCP at baseline and during the follow-up period. Eligible study subjects also had at least one A1C level drawn within 3 months before the June 2005 medication list ascertainment (baseline A1C) and at least one additional A1C drawn during the follow-up year (July 2005–June 2006).

We conducted a prospectively analyzed cohort study to identify factors predicting disease progression in the subset of patients with type 2 diabetes who had A1C <7% and were not on glucose-lowering medications at study baseline (n = 705). Clinical disease progression was defined as either being started on any glucose-lowering medications or having A1C ≥7% at 1-year follow-up, whereas nonprogression was defined as A1C <7% and not on any medication therapy at 1-year follow-up. We considered the transition from good A1C control off medications to requiring glucose-lowering medications as indication of clinical disease progression regardless of A1C. This definition accounts for subjects whose worsening ability to self-regulate their glycemic control has been masked by the addition of glucose-lowering medications. Among the subset of patients whose diabetes progressed (n = 200), we examined factors associated with initiation of glucose-lowering medication.

A1C levels were measured at the Massachusetts General Hospital (MGH) diabetes laboratory using a high-performance liquid chromatography method (15). The coefficient of variation for the high and low standard value is <2.5%. The MGH A1C assay is protected against temporal drift through the use of long-term quality control samples and is a primary reference lab for the National Glycohemoglobin Standardization Program (16).

Statistical methods

The *t* test was used for univariate analysis of normally distributed continuous variables and the χ^2 test for analysis of discrete variables. We created separate multivariate logistic regression models to identify variables independently associated with our two outcomes of interest: odds of progression and odds of medication initiation among progressors. A two-sided *P* value <0.05 was considered statistically significant. Statistical analyses were performed using the SAS version 9.1 statistical software package. The study was approved by the MGH/Partners Health Care System Institutional Review Board.

Results

We identified 5,804 type 2 diabetic patients who met our inclusion criteria and had 2 complete years of follow-up. Of these patients, 998 (17.2%) were not prescribed any hypoglycemic medicines at the baseline visit. The 705 (71%) patients in this subset who had A1C levels <7% (mean A1C ± SD 6.24 ± 0.47%) are the subjects of our primary longitudinal analysis. Of these 705 patients, 228 (32.2%) had an A1C in the normal range (<6.1%).

Predictors of disease progression

Twenty-eight percent of the patients (200 of 705) had disease progression at 1 year follow-up (mean A1C ± SD 6.54 ± 0.3% at baseline, 7.28 ± 0.9 at follow-up). Univariate predictors of disease progression in these 705 patients are summarized in Table 1. In univariate analyses, risk factors for deterioration included higher baseline A1C ($P < 0.001$), nonwhite race ($P = 0.04$), and lower baseline HDL ($P = 0.01$). Only 15 (7.5%) of the 200 progressors had A1C <6.1% at baseline. Obesity at baseline, baseline weight or BMI, and history of hypertension were not associated with diabetes progression at follow-up. In multivariate analyses, baseline A1C ($P < 0.0001$) and younger age were the major independent predictors of progression after adjusting for race, sex, and baseline HDL levels. Each decade of age reduced the risk of progression by 15% (OR0.85 [95% CI0.73–0.99], $P = 0.04$). In a separate model that included change-from-baseline variables, each 1-lb increase in weight was associated with a 2% increased odds of progression (1.02 [1.002–1.037], $P = 0.03$).

Predictors of treatment initiation among progressors

Of the 200 progressors, 39% (77 of 200) remained untreated with glucose-lowering medications despite having an A1C ≥7%. Among the 123 patients started on therapy, metformin (64.2%), sulfonylureas (27.6%), and insulin (9%) were the most commonly prescribed drugs. Of the 123 treated subjects at follow-up, 51 subjects (41.5%) had A1C <7%. The mean A1C of treated subjects was 7.26 ± 1.12% compared with 7.3 ± 0.33% for progressors who remained untreated and 6.23 ± 0.47% for nonpro-gressors. Baseline characteristics of progressors started on medication therapy compared with progressors not started on therapy are listed in Table 2.

Compared with untreated patients, treated patients were younger (60.5 ± 12.1 vs. 69.5 ± 12.8 years, $P < 0.001$) and more likely to be nonwhite (75.4 vs. 55.9%, $P = 0.01$). Patients with commercial insurance and Medicaid were more likely to be started on therapy than patients on Medicare ($P = 0.02$). In multivariate analyses, after adjusting for race, sex, and weight

change, the likelihood of medication initiation decreased by 40% (OR 0.6 [95% CI 0.39–0.92], $P = 0.02$) with every decade of age and decreased by 2.3% (0.98 [0.96–1.0], $P = 0.02$) with each 1-mg/dl decrease in baseline LDL level. Concurrent cardiovascular disease did not affect the likelihood of initiation of diabetes medications.

A sensitivity analysis with "disease progression" defined solely based on A1C ≥7% (i.e., excluding patients who were started on therapy in period 2 and remained with A1C <7% at follow-up) resulted in similar results after accounting for negative confounding by age.

Conclusions

In this study, we performed a longitudinal analysis of a primary care cohort of type 2 diabetic patients with A1C <7% at baseline to identify factors associated with disease progression and, among those patients who progressed, with medication initiation. We found that patients with A1C levels closer to 7%, younger patients, and those gaining weight progressed more often than older patients and patients who did not gain weight. Among patients whose glycemic control worsened over the subsequent year, younger age and higher LDL levels were associated with initiation of glucose-lowering medication.

The association of younger age with diabetes progression in this usual care cohort provides indirect evidence that the pathogenesis of type2 diabetes in subjects who develop diabetes at a younger age is different from that of older subjects. Indeed, some studies suggest that older type 2 diabetic patients are more likely to be insulin resistant than younger type 2 diabetes subjects, while younger nonobese subjects with type 2 diabetes tend to be more insulin deficient (17–19). Given the increased rate of type 2 diabetes progression among younger compared with older subjects seen in clinical trials and in the usual-care environment, younger patients with diabetes should be managed more aggressively with earlier initiation of medications.

Race/ethnicity did not independently predict diabetes progression in our study. Furthermore, there were no race/ethnic differences in the proportion of patients initiated on therapy at 1-year of follow-up. Patients in our analysis were all cared for within the same academic primary care network, which may have attenuated system-level disparities that are evident in national analyses (20).

Our data also differ somewhat from the National Health and Nutrition Examination Study (NHANES) data, which suggest that poor glycemic control (A1C >8%) was more common in non-Hispanic black women and Mexican-American men compared with other groups (11). A recently published metaanalysis similarly observed higher A1C among African Americans compared with non-Hispanic whites with diabetes (21). However, another study found that after adjusting for socio-demographic and other variables, race was not significantly associated with poor glycemic control (9).

Prior studies have shown an association between smoking and risk for developing type 2 diabetes (22,23); however, no studies have specifically examined the relationship between smoking and type 2 diabetes progression. In our analysis, we identified a significant association of smoking with disease progression that was eliminated in multivariate analysis after adjusting for age, baseline A1C, sex, baseline HDL, and race. Larger studies may be needed to rule out definitively a direct influence of smoking on deterioration in glycemic control.

Lack of medication intensification (so called "clinical inertia") has been identified as an important barrier to effective diabetes management (24,25). In our study, over two-thirds of patients whose A1C levels increased to ≥7% were started on medication therapy in the

follow-up year. This relatively high rate of response to worsening glycemia contrasts with that in prior studies, suggesting that physicians have become more aggressive in general or that the PCPs in the current study were more aggressive. Older patients in our analysis were less likely than younger patients to be started on hypoglycemic therapy, evidence that PCPs may be treating younger patients more aggressively than older patients.

Surprisingly, diagnosis of coronary artery disease and history of other cardiovascular risk factors including hypertension, smoking, and obesity did not predict more aggressive diabetes management in multivariate analysis, even though coprevalence of cardiovascular risk factors implies the need for more aggressive glycemic control.

This study is one of the first studies to use “usual care” clinical data to assess risk factors for disease progression in untreated patients with type 2 diabetes. Although conducted within a single large primary care network covering eastern Massachusetts, the patient population seen at these primary care clinics included a wide range of ages, race/ethnicities, and socio-economic status. Results of our study underscore the ongoing need to improve diabetes management and can be used to encourage changes.

Our results must be interpreted within the context of the study design. All physicians in the three practice settings (academic practice, health center, and private office) are members of the same hospital-based physician's organization, share the same electronic medical record, and have similar access to hospital-based disease management resources. However, even though we could assume that all subjects received baseline education on therapeutic lifestyle changes, we were unable to evaluate adherence to medication or lifestyle modification, factors that may have influenced the decision to initiate therapy. Furthermore, this study assumes that the patients received all their care within our clinical network. This assumption is justified by a prior study of our population that showed that patients with recurrent visits to their primary care provider tend to receive all of their care in our system (13). In addition, while the tendency to progress is likely to be generalizable to other patient populations, patterns of care in academic health centers may be less generalizable to other settings. We were unable to obtain family history of diabetes on most of the subjects in the registry. Family history may be useful for the prediction of future impairment in β-cell function and progression of diabetes. However, for our current analysis the primary goal was to apply clinical data readily available from clinical care databases to predict subsequent disease progression and treatment initiation. Lastly, we were not able to directly measure diabetes duration. Diabetes duration has been associated with glycemic control in some studies (9,10). Type 2 diabetes is well known to be a progressive disease over time, and although the selection of subjects who are not on any therapy for type 2 diabetes and with A1Cs <7% suggests that they are relatively early in the course of their disease, we cannot establish the date of onset of type 2 diabetes. The exact date of onset of type 2 diabetes is difficult to establish with accuracy, and a significant proportion of patients remain undiagnosed (26).

In summary, we have shown that more than 25% of patients with type 2 diabetes on no hypoglycemic agents and with A1C <7% at baseline experience progression of their disease at 1 year. Over one-third of patients who cross the A1C threshold of 7% remained untreated. Older patients were less likely to be started on therapy, and CVD risk did not predict more aggressive glycemic management. These findings support more aggressive management of type 2 diabetic patients who gain weight and who are younger, as they appear to be more likely to progress. Conversely, there may be an identifiable subset of older patients with stable weight who may be followed without initiating metformin therapy.

Acknowledgments

L.N.P. is supported by a postdoctoral training grant (T32). D.M.N. is supported in part by the Earl. P. Charlton Fund for Innovative Diabetes Research. R.W.G. is supported by a National Institute of Diabetes and Digestive and Kidney Diseases Career Development Award (K23 DK067452).

Parts of this study were presented in abstract form at the 67th annual meeting of the American Diabetes Association, Chicago, IL, 22–26 June 2007.

We acknowledge Ms. Nancy Wong for programming assistance.

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Abbreviations

MGH	Massachusetts General Hospital
PCP	primary care physician.

Table 1

Baseline patient characteristics associated with diabetes progression* over the subsequent year (*n* = 705)

	Nonprogressors	Progressors	*P*†
n	505	200	
Demographic characteristics			
Age (years)	65.5 ± 14	64 ± 13.1	0.2
White race	400 (79.2)	143 (71.5)	0.03
Female sex	267 (52.9)	94 (47.0)	0.16
Primary care site			
Health center	195 (40.0)	70 (36.3)	
Hospital based	250 (51.3)	101 (52.3)	
Private practice	42 (8.6)	22 (11.4)	
<8 medications	245 (48.5)	107 (53.5)	0.23
Insurance type			
Commercial	180 (35.6)	63 (31.5)	
Medicaid	37(7.33)	25(12.5)	
Medicare	272 (53.9)	105 (52.5)	
Uninsured	16 (3.2)	7 (3.5)	
Estimated household income (USD)	58,018 ± 41,821	55,065 ± 31,824	0.32
Comorbid illness: known history of			
Hyperlipidemia	293 (58.0)	117 (58.5)	0.91
Hypertension	364 (72.1)	138 (69.0)	0.42
Smoking	92 (18.2)	26 (13.0)	0.09
Obesity	128 (25.4)	58 (29.0)	0.32
Coronary artery disease	111 (22.0)	43 (21.5)	0.89
Aspirin use	238 (47.1)	87 (43.5)	0.38
Clinical characteristics			
Baseline weight (lb)	187.1 ±43.1	194.7 ± 53.7	0.16
Baseline BMI (kg/m^2)	32 ± 6.9	32.3 ± 9.3	0.78
Change in weight (lb)	−2.0 ± 16.6	0.5 ± 15.8	0.17
Baseline SBP (mmHg)	129.3 ± 17.6	127.9 ± 16.5	0.36
Baseline DBP (mmHg)	74.7 ± 11.3	73.8 ± 10.9	0.36
Laboratory measurements			
Baseline LDL (mg/dl)	94.4 ± 30.9	94.8 ± 31.9	0.89
Baseline HDL (mg/dl)	51.2 ± 15.7	47.7 ± 13.9	<0.01
Baseline triglycerides (mg/dl)	146.1 ± 109.2	164.1 ± 100.3	0.06
Baseline A1C (%)	6.12 ± 0.5	6.54 ± 0.3	<0.01
Albuminuria‡			0.21
Unknown	146 (28.9)	70 (35.0)	
Absence	283 (56.0)	110 (55.0)	
Microalbuminuria	58 (11.5)	16 (8.0)	

	Nonprogressors	Progressors	$P^{\dagger}$
Macroalbuminuria	18 (3.6)	4 (2.0)	

Data are means ± SD or *n* (%).

*Diabetes progression is defined as having an A1C increase from <7% at baseline to ≥7% at follow-up or the initiation of a hypoglycemic agent at follow-up, suggesting a response to worsening glycemia.

†*t* test comparing nonprogressors and progressors.

‡Microalbuminuria = urine albumin excretion 30–300 mg/g creatinine, macroalbuminuria = urine albumin excretion >300 mg/g creatinine. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2

Baseline characteristics associated with initiation of therapy among patients whose disease progressed[*] (*n* = 200)

	Started on treatment	Not started on treatment	*P*[†]
n	123	77	
Demographic characteristics			
Age (years)	60.5 ± 12.1	69.5 ± 12.8	<0.01
White race	80 (65.0)	63 (81.8)	0.01
Female sex	60 (48.8)	34 (44.2)	0.52
Primary care site			0.96
Health center	43 (35.5)	27 (37.5)	
Hospital based	64 (52.9)	37 (51.4)	
Private practice	14 (11.6)	8 (11.1)	
<8 medications	64 (52.0)	43 (55.8)	0.60
Insurance type			0.02
Commercial	42 (34.1)	21 (27.3)	
Medicaid	21 (17.1)	4 (5.2)	
Medicare	55 (44.7)	50 (64.9)	
Uninsured	5 (4.1)	2 (2.6)	
Estimated household income (USD)	53,341 ± 27,905	57,808 ± 37,260	0.37
Comorbid illness: known history of			
Hyperlipidemia	68 (55.3)	49 (63.6)	0.24
Hypertension	79 (64.2)	59 (76.6)	0.07
Smoking	18 (14.6)	8 (10.4)	0.39
Obesity	36 (29.3)	22 (28.6)	0.92
History of coronary artery disease	22 (17.9)	21 (27.3)	0.12
Aspirin use at baseline	48 (39.0)	39 (50.7)	0.11
Clinical characteristics			
Baseline weight (lb)	195.8 ± 45.4	193.1 ± 64.4	0.80
Baseline BMI (kg/m^2)	32.6 ±7.1	31.7 ± 12.1	0.72
Change in weight (lb)	−1.0 ± 17.0	2.8 ± 13.7	0.23
Baseline SBP (mmHg)	126.0 ± 14.9	130.7 ± 18.2	0.09
Baseline DBP (mmHg)	72.4 ± 10.1	75.7 ± 11.8	0.07
Laboratory measurements			
Baseline LDL (mg/dl)	95.9 ± 34.5	92.9 ± 27.2	0.54
Baseline HDL (mg/dl)	46.1 ± 12.5	50.5 ± 15.7	0.05
Baseline triglycerides (mg/dl)	165.4 ± 104.4	161.8 ± 93.9	0.82
Baseline A1C (%)	6.5 ± 0.3	6.6 ± 0.28	0.07
Albuminuria[≠]			0.08
Unknown	35 (28.5)	35 (45.5)	
Absence	74 (60.2)	36 (46.8)	
Microalbuminuria	12 (9.8)	4 (5.2)	

	Started on treatment	Not started on treatment	$P^{\dagger}$
Macroalbuminuria	2 (1.6)	2 (2.6)	

Data are means ± SD or *n* (%).

*Diabetes progression is defined as having an A1C increase from <7% at baseline to ≥7% at follow-up or the initiation of a hypoglycemic agent at follow-up, suggesting a response to worsening glycemia.

†*t* test comparing nonprogressors and progressors.

‡Microalbuminuria = urine albumin excretion 30–300 mg/g creatinine, macroalbuminuria = urine albumin excretion >300 mg/g creatinine. DBP, diastolic blood pressure; SBP, systolic blood pressure.