Proactive Case Management of High-risk Patients With Type 2 Diabetes Mellitus by a Clinical Pharmacist: A Randomized Controlled Trial

Hae Mi Choe, PharmD; Sonya Mitrovich, MD; Daniel Dubay, MD; Rodney A. Hayward, MD; Sarah L. Krein, PhD, RN; and Sandeep Vijan, MD

Objective: To evaluate the effect of case management by a clinical pharmacist on glycemic control and preventive measures in patients with type 2 diabetes mellitus.

Study Design: Randomized controlled trial in a university-affiliated primary care internal medicine clinic.

Methods: We recruited 80 patients with poorly controlled type 2 diabetes mellitus. A clinical pharmacist provided evaluation and modification of pharmacotherapy, self-management diabetes education, and reinforcement of diabetes complications screening processes through clinic visits and telephone follow-up. The main clinical outcome was hemoglobin A_{1c} (HbA_{1c}) level; process measures included HbA_{1c} and low-density lipoprotein measurement, retinal examination, urine microalbumin testing (or use of angiotensin-converting enzyme inhibitors), and monofilament screening for diabetic neuropathy.

Results: Patients in the intervention and control groups were similar in age, sex, mean HbA_{1c} levels (10.1% and 10.2%, respectively; $P = .65$), and current treatment regimens at baseline. Patients who received case management by the clinical pharmacist achieved greater reduction in HbA_{1c} levels than those in the control group (2.1% vs 0.9%, $P = .03$). Three of the 5 process measures were conducted more frequently in the intervention group than the control group, including low-density lipoprotein measurement (100.0% vs 85.7%, $P = .02$), retinal examination (97.3% vs 74.3%), and monofilament foot screening (92.3% vs 62.9%).

Conclusions: Proactive diabetes case management by a pharmacist substantially improved glycemic control and diabetes process-of-care measures. This approach, integrated with and based in the primary care setting, was an effective and efficient approach to improving care, especially for those with poor glycemic control at baseline.

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Type 2 diabetes mellitus is a highly prevalent condition that has substantial associated morbidity, mortality, and healthcare costs. Diabetes mellitus affects approximately 18 million Americans,[1] and these numbers are expected to rise during the next several decades because of the increasing age and prevalence of obesity in the US population.[1,2] People with diabetes mellitus die of cardiovascular disease at 2 to 3 times the rate of age- and sex-matched control subjects,[3-7] and the microvascular complications of diabetes mellitus make it the leading cause of preventable blindness, renal disease, and amputation in industrialized nations.[8-10] These complications have dramatic implications for healthcare costs; indeed, diabetes mellitus led to about $132 billion in direct and indirect costs in 2002 in the United States,[11] and the cost to healthcare plans is at least 2 to 3 times that of age-matched patients without diabetes mellitus.[12,13]

A substantial amount of diabetes-related morbidity can be prevented through increased use of current management guidelines and application and increased monitoring of available therapies, ranging from intensive blood pressure[14-16] and glycemic[17-19] control to the use of preventive measures such as retinal screening.[20-22] Although there are effective therapies to prevent diabetes complications, it is also clear that there are several barriers to providing optimal diabetes care in the primary care setting.[23-25] The complex and varied nature of diabetes-related interventions makes it difficult to achieve multiple goals in limited visits, particularly in the current environment in which providers are increasingly allotted less time with patients. Furthermore, many diabetes treatment goals are heavily dependent on patient self-management and lifestyle changes. Therefore, providers are often left with the difficult task of trying to manage a complex multisystem and patient-centered disease in a health system that is poorly designed to manage chronic diseases that require frequent, intensive follow-up and detailed patient counseling and education.

Case management is one of the most commonly suggested methods to improve chronic disease manage-

From the College of Pharmacy (HMC) and Department of Internal Medicine (SM, DD, RAH, SLK, SV), University of Michigan; Ann Arbor Veterans Affairs Center for Practice Management and Outcomes Research (RAH, SLK, SV); and Michigan Diabetes Research and Training Center (RAH, SLK, SV); Ann Arbor, Mich.

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Address correspondence to: Sandeep Vijan, MD, MS, Ann Arbor Veterans Affairs Center for Practice Management and Outcomes Research, 2215 Fuller Road, Mailstop 11H, Ann Arbor, MI 48105. E-mail: svijan@umich.edu.

ment.[26,27] Case management has been defined as a collaborative process that assesses, plans, implements, coordinates, monitors, and evaluates the options and services required to meet an individual's health needs, using communications and available resources to promote quality, cost-effective outcomes.[28] Case management can be implemented in different forms, including using nurses (nurse practitioners or certified nurse specialists), physician assistants, social workers, and pharmacists, and the nature of the intervention can range from autonomous medication management (in the case of pharmacists or primary care personnel with prescribing privileges) to telephone-based counseling or algorithm-based disease management recommendations to primary care providers. However, there has been little rigorous evaluation of case management for patients with diabetes mellitus, and results have been variable.[29,30] Indeed, a recent randomized trial found no benefit of case management in a high-risk population of patients with diabetes mellitus, raising concerns about the optimal structure and implementation of case management systems.[31,32]

In particular, pharmacist-based case management has not been rigorously evaluated among patients with diabetes mellitus, although results of short-term trials and observational studies have been encouraging.[33-36] Pharmacist-based case management has, however, been proven to be successful for management of congestive heart failure and anticoagulation therapy.[37-39] In the case of diabetes, the complex nature of medication management would seem an ideal opportunity for using a clinical pharmacist as a case manager. Pharmacists offer particular strengths in these situations, given the frequent polypharmacy among patients with diabetes mellitus, risks of adverse drug events, and drug interactions. Therefore, we conducted a randomized controlled trial of the effectiveness of a pharmacist-based case management intervention in a general internal medicine clinic setting.

METHODS

Study Design and Setting

We conducted a randomized controlled trial of a diabetes quality improvement intervention using a clinical pharmacist (HMC) to assist primary care providers in the management of patients with type 2 diabetes mellitus. The study was conducted at a university-affiliated ambulatory care clinic that has 10 primary care internists as its primary care staff, all of whom agreed to have their patients contacted for possible participation in the study. The study design was intended to reflect, as much as possible, real-world effectiveness and to minimize the influence of the clinical pharmacist on usual practice. Therefore, the control group was kept as a natural control; that is, they received only regular care, including regular follow-up visits with their primary care physicians. The control group received no special contact during the intervention and did not have exit interviews or process measurements at the end of the study. The study was approved by the University of Michigan Medical School Institutional Review Board for Human Subjects Research.

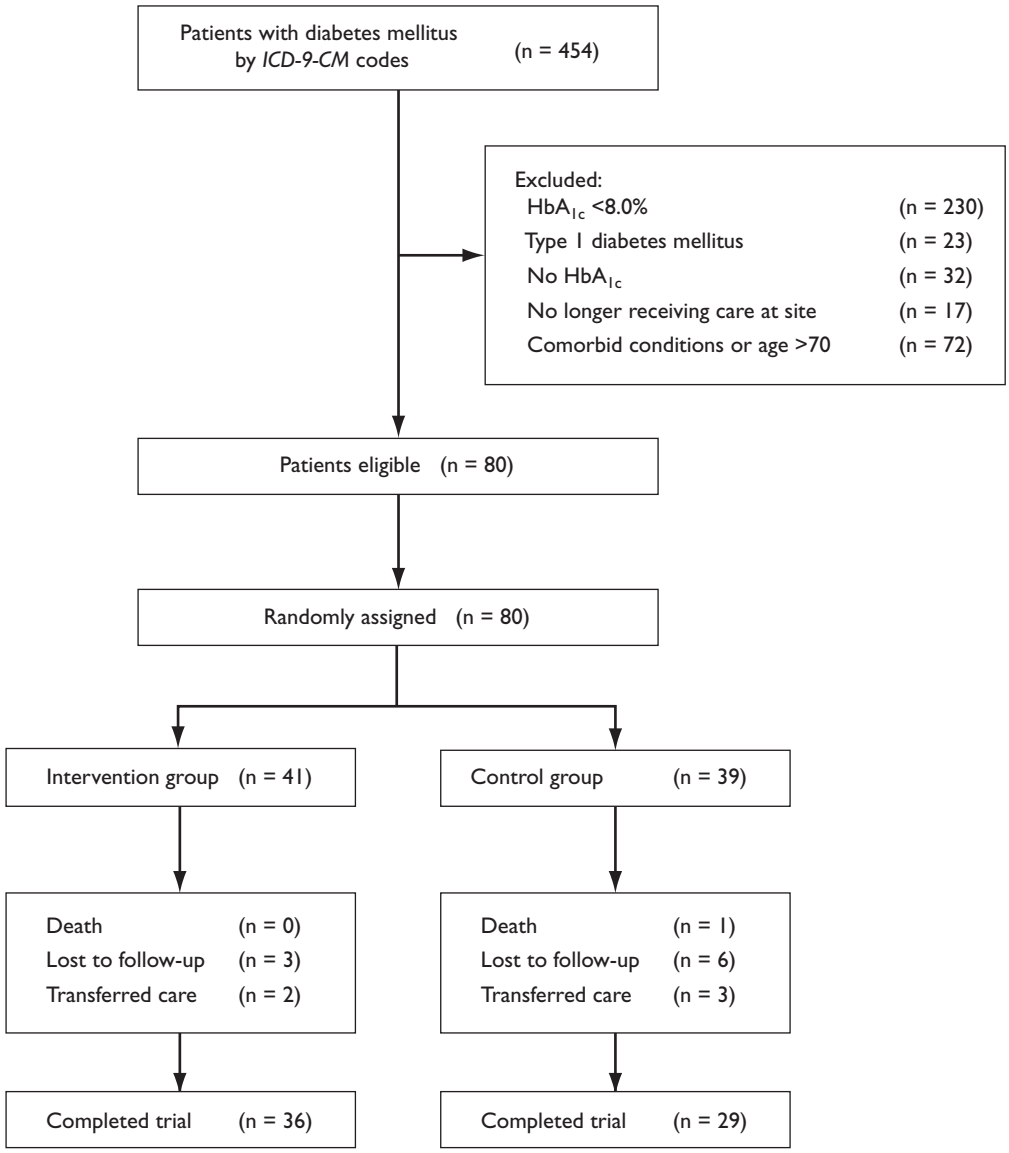
Patients and Randomization

We based our sample size calculations on the assumption that the effect size of the intervention would be a change in hemoglobin A_{1c} (HbA_{1c}) level of 1.1%, the difference found in a prior study[30] of case management. An initial exploratory analysis of laboratory data at the intervention site showed that high-risk patients with diabetes mellitus (ie, HbA_{1c} levels, ≥ 8.0%) had a mean ± SD HbA_{1c} level of 10.1% ± 1.7%. Based on these numbers, we calculated that we would need 38 patients in each study arm to have 80% power to detect a 1.1% difference in HbA $level_{1c}$ with a 2-tailed $P < .05$.

We identified 454 patients with diabetes mellitus at the study site, using *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes. Patients who were eligible for study enrollment were the 80 high-risk individuals whose most recent HbA_{1c} levels were 8.0% or greater. We selected this group of patients because they are at particularly high risk for adverse diabetes outcomes and are likely to receive the most benefit from intensified glucose control and from preventive interventions such as eye screening.[19,20,40,41] Patients were excluded from the study if they had type 1 diabetes mellitus (based on diagnosis before age 30 years), if they were older than 70 years, or if they were diagnosed as having cancer, renal failure, severe cirrhosis, malignant hypertension, or a severe concurrent illness that would substantially limit life expectancy or require extensive systemic treatment. The trial flow diagram is shown in the **Figure.** Recruitment was coordinated through and with the approval of the primary care physicians; this led to essentially no refusal to participate, so that the full sample of eligible patients was enrolled, although several patients in each study arm dropped out as the study progressed. Eighty patients were enrolled and randomized to the control group or the intervention group. To ensure balanced randomization across levels of glycemic control, patients were stratified into 4 groups based on the baseline HbA_{1c} levels (8.0%-8.9%, 9.0%-9.9%, 10.0%-10.9%, and ≥11.0%) and were randomized

to the intervention group or control group within each stratified group.[42] Randomization within each stratum was simple: because the study was small, randomization was done by hand, drawing numbers from a container that included "0" for the control group or "1" for the intervention group.[43] Given the nature of the intervention, patients, providers, and the case manager were not blinded to the intervention.

Figure 1. Trial Flow Diagram



ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*; HbA_{1c}, hemoglobin A_{1c}.

Outcome Measures

The primary outcome measure for this study was change in HbA_{1c} level. The HbA_{1c} level (reference range, 3.8%-6.4%) was measured using a high-performance liquid chromatography machine (Tosoh Corporation, Montgomeryville, Pa). Because this project was designed to measure real-world effectiveness, there were no specific exit interviews or follow-up laboratory testing mandated by the protocol; rather, the interaction between the clinical pharmacist and the primary care physicians determined the frequency and timing of laboratory measures and interventions, based on their clinical judgment of patient needs. Therefore, we used the first HbA_{1c} level measured after the 12-month intervention as the primary outcome measure. Patients were allowed up to 24 months after enrollment to obtain the final HbA_{1c} measurement.

Secondary outcome measures included rates of diabetes process measures, including low-density lipoprotein measurement, dilated retinal examination, urine microalbumin screening (or use of angiotensin-converting enzyme inhibitors), and monofilament testing for diabetic neuropathy. Performance of these tests within the 2-year time frame of the study was determined by medical chart review by a single reviewer, using a standardized abstraction form. The rate of HbA_{1c} measurement was also used as a process measure, although

HbA_{1c} level was assessed at 1 year because it was the primary study outcome and measurement was dictated by protocol in the intervention group after the 1-year intervention.

Intervention

The intervention was conducted in a university-affiliated primary care clinic. The case manager was a clinical pharmacist who was already established as a pharmacotherapy consultant at the clinic before the start of the intervention. It was hypothesized that her established relationship with the primary care physicians and some of the patients would foster a level of cooperation and trust that would allow the intervention to be a collaborative process. Of note, there is no on-site diabetes education program in this clinical setting, although referral-based programs are available.

The clinical pharmacist evaluated patients' therapeutic regimens based on efficacy, safety, adverse effects, drug interactions, drug costs, and monitoring. All therapeutic recommendations were discussed with the primary care physicians before significant therapy alterations. The clinical pharmacist followed up on disease management and medication management protocols approved by the primary care physicians. The protocols were based on those used in a prior study[30] but were updated to account for new pharmacologic agents (ie, thiazolidinediones) and were intended to provide guidance rather than to serve as inflexible protocols. This allowed the clinical pharmacist to have some autonomy in decision making and to use her clinical knowledge and pharmacology expertise to care for the patients. However, this approach to case management differs from that in prior investigations in that it also involved brief face-to-face consultations between the pharmacist and the primary care physicians, creating a team-based approach to management rather than having a centralized case manager under the direction of 1 or 2 supervising specialists. Because the clinical pharmacist was on site as an active member of the healthcare team, the primary care physicians had access to discuss nonintervention cases; this may have caused some cross-contamination in the groups, although this would bias the study results toward the null.

Intervention patients had an initial clinic visit with the clinical pharmacist that lasted approximately 1 hour. During this visit, in addition to an initial assessment of medication management, the clinical pharmacist provided patients with basic education regarding diabetes self-management skills. This included an emphasis on the importance of self-care, medications, and screening processes. Subsequent visits were scheduled based on therapeutic alterations and educational needs. Generally, the clinical pharmacist contacted the patients by telephone on a monthly basis, unless more frequent assessment or recommendations were needed, and saw the patients in conjunction with their routine primary care visits. The clinical pharmacist also periodically reviewed the status of all intervention patients and provided condensed "diabetes status updates" to providers using a standardized form (available from the author).

Table 1. Baseline Characteristics of the Study Population*

Characteristic	Control Group	Intervention Group	*P*
Age, y	51.0 ± 9.0	52.2 ± 11.2	.60†
Male sex	46.1	48.8	.81†
Race			.10§
White	71.8	80.5	
African American	12.8	17.1	
Other	5.1	2.4	
Unknown	10.3	0.0	
Baseline hemoglobin A_{1c} level, %	10.2 ± 1.7	10.1 ± 1.8	.65‡
Glycemic management			.58§
No hypoglycemic medications	20.5	12.2	
Sulfonylurea	23.1	24.3	
Metformin hydrochloride	10.3	12.2	
Sulfonylurea + metformin	15.4	22.0	
Insulin (alone or with oral agents)	30.8	29.3	
Insurance type			.62§
Medicare	10.3	9.8	
Private insurance	89.7	87.8	
None	0.0	2.4	

*Data are given as means ± SDs or as percentages unless otherwise indicated.
†Based on 2-sample *t* test.
‡Based on Wilcoxon rank sum test.
§Based on contingency table analysis and χ^2 test.

Statistical Analysis

For the primary outcome measure, HbA_{1c} level, we compared the baseline lev-

els, final levels, and change scores (calculated by subtracting the final from the baseline HbA_{1c} levels) using Wilcoxon rank sum tests. The change in HbA_{1c} levels was also evaluated using linear regression analysis. Because analysis of residuals demonstrated substantial heteroskedasticity, we used Huber-White estimators of standard errors.[44,45] In these regression analyses, we used the final HbA_{1c} level as the dependent variable; independent variables included an indicator variable for the intervention and the baseline HbA_{1c} level. We also conducted analyses controlling for differences in follow-up intervals (because of the nature of the control group). Last, we tested an interaction term between the baseline HbA_{1c} level and the intervention to assess whether the response to the intervention varied based on the initial level of glycemic control.

All analyses were performed based on intention to treat and at a significance level of $P < .05$. In the primary analyses, missing data were assumed to be missing at random. Notably, the only missing final results were among unavailable patients who dropped out of the trial because of loss to follow-up, transfer, or death. However, we also conducted sensitivity analyses for missing final HbA_{1c} values by imputing these values based on the baseline values and repeating the analyses. As an additional sensitivity analysis, we repeated the analyses, assuming that, for those with missing final HbA_{1c} data, there was no change in initial HbA_{1c} values. All data analyses were conducted using Stata version 7.0 (Stata Corporation, College Station, Tex).

RESULTS

The study sample consisted of 41 patients randomized to the intervention group and 39 patients randomized to the control group. The baseline characteristics of the intervention and control groups are shown in **Table 1.** The mean baseline HbA_{1c} level in the intervention group was 10.1% and in the control group was 10.2%. There were no statistically significant differences in the distribution of demographic characteristics and medication use between the groups. Nearly all patients had health insurance, mostly through private third-party payers.

The primary outcome measure of the study was HbA_{1c} level. Because of the nature of the control group, the follow-up interval for obtaining the final HbA_{1c} measurement was slightly shorter in the intervention group than the control group (13.6 vs 14.9 months, $P = .046$). Dropout rates were also slightly lower in the intervention group than the control group. In the intervention group, no patients died, 3 were lost to follow-up, and 2 transferred to a different healthcare provider. In the control group, 1 patient died, 6 were lost to follow-up, and 3 transferred to a different healthcare provider.

The effect of the clinical pharmacist–based management on change in HbA_{1c} levels is shown in **Table 2.** The mean decrease in HbA_{1c} levels in the intervention group was –2.1% (from 10.1%-8.0%) and in the control group was –0.9% (from 10.2%-9.3%). Therefore, the mean difference in HbA_{1c} change scores between the intervention and control groups was 1.2% ($P = .03$), and the mean difference in final HbA_{1c} values was 1.3% ($P = .01$). These differences persisted after adjusting for differences in duration of follow-up between the intervention and control groups using linear regression analysis (mean difference in HbA_{1c} change scores between groups, 1.1%; $P = .04$). Likewise, greater improvement among intervention patients was still observed when we imputed missing final HbA_{1c} values for patients who were lost to follow-up (mean difference in HbA_{1c} change scores between groups, 1.0%; $P = .04$) or when it was assumed that there was no change in HbA_{1c} level among those who were lost to follow-up (mean difference in HbA_{1c} change scores between groups, 1.2%; $P = .01$).

We found a strong statistical interaction between the intervention and baseline HbA_{1c} levels ($P < .001$), suggesting that patients with higher HbA_{1c} levels at enrollment had a greater improvement in glycemic control than those with more moderate elevations. The mean changes in HbA_{1c} levels, stratified by the baseline HbA_{1c} values, are shown in **Table 3.** These findings demonstrate that those with poor glycemic control at baseline received most of the benefit of the intervention; indeed, patients who had only moderate elevations in HbA_{1c} levels had minimal response. For example, patients with initial HbA_{1c} levels of 8.0% received virtually no benefit from the intervention, while those with initial HbA_{1c} levels of 10.0% had about a 1.5% decrease in HbA_{1c} levels attributed to the intervention (a decrease of 2.1% in the intervention group and 0.6% in the control group).

Table 2. Decrease in Hemoglobin A_{1C} (HbA_{1C}) Levels During 12- to 24-Month Follow-up*

HbA_{1c} Level, %	Control Group	Intervention Group	$P^{\dagger}$
Baseline	10.2 ± 1.7	10.1 ± 1.8	.65
Final	9.3 ± 2.1	8.0 ± 1.4	.01
Decrease	0.9 ± 2.0	2.1 ± 2.5	.03

*Data are given as means ± SDs unless otherwise indicated. Results were unchanged by adjusting for duration of follow-up using linear regression analysis.
†Based on Wilcoxon rank sum test.

Table 3. Variation in Response to the Intervention by Baseline Hemoglobin A_{1c} (HbA_{1c}) Levels

Baseline HbA_{1c} Level, %	Decrease in HbA1c Level, mean %*		
	Control Group	Intervention Group	Improvement Attributable to Intervention
8.0	0.2	0.2	0.0
9.0	0.4	0.8	0.4
11.0	1.5	2.9	1.4
13.0	2.3	5.9	3.6

*Based on the calculation of posterior values using linear regression models.

The effect of the clinical pharmacist's management on rates of diabetes process-of-care measures is shown in **Table 4.** Low-density lipoprotein measurement (100.0% vs 85.7%, $P = .02$), retinal examination within 2 years (97.3% vs 74.3%, $P = .004$), and documented monofilament examination for neuropathy (92.3% vs 62.9%, $P = .002$) occurred more frequently among those in the intervention group compared with the control group. Rates of HbA_{1c} measurement and microalbuminuria screening (or use of angiotensin-converting enzyme inhibitors) were not different between the 2 groups, although the trends favored the intervention patients.

DISCUSSION

Case management for chronic diseases such as diabetes mellitus is being recommended and adopted at a rapid rate. Although there are clear needs for improved disease management to improve outcomes of care, and possibly to decrease costs related to diabetes-related complications, there is to date little rigorous evaluation of the effectiveness of disease management programs in real-world settings.

Indeed, in the case of diabetes, rigorous evaluation of case management has been limited primarily to the use of nurses as case managers. One randomized study[29] reported modest improvements in glycemic control; this study was designed to be a low-intensity intervention, with the nurse case manager providing patient education and facilitating compliance through telephone contacts. A second randomized study[30] found that more intensive case management led to a significant improvement in glycemic control. In this study, the nurse case manager had direct management responsibilities, including medication management under a protocol. However, the study was limited by substantial differential dropout, with many more patients lost to follow-up in the intervention arm than the control arm; therefore, the results may have been biased in favor of the intervention. A third investigation, and the most rigorously designed, found that nurse practitioner–based case management of patients with diabetes mellitus had no effect on any clinical outcomes, although patient satisfaction was improved.[31,32]

Other models of case management have not been well evaluated among patients with diabetes mellitus. Our study demonstrates that a pharmacist acting as a case manager can improve glycemic control and the use of recommended screening procedures among high-risk patients with type 2 diabetes mellitus. The group assigned to case management by a pharmacist achieved a 1.2% greater reduction in HbA_{1c} levels than the control group and had 15% to 30% improvements in the percentages of patients completing recommended screening. Based on findings of the Diabetes Control and Complications Trial research group and the UK Prospective Diabetes Study group, this improvement in HbA_{1c} levels would be expected to lead to 40% to 50% relative reductions in the risk of intermediate and advanced microvascular complications, although this level of improvement would need to be sustained for a long period before substantial improvements in outcomes would be seen.[18,19,46,47] Interestingly, we found that the intervention was mainly effective for those with poor baseline glycemic control. This finding that it is much easier in real-world practice to achieve moderate than

Table 4. Comparison of Rates of Process Measures*

Process Measure	Control Group	Intervention Group	$P^{\dagger}$
Hemoglobin A_{1c} measurement	82.9	92.3	.21
Low-density lipoprotein measurement	85.7	100.0	.02
Retinal examination within 2 years	74.3	97.3	.004
Urine albumin screen (or use of angiotensin-converting enzyme inhibitor)	85.7	94.9	.18
Documented monofilament foot examination	62.9	92.3	.002

*Unless otherwise indicated, data are given as percentages among 74 study patients with measurements (excludes 5 patients who transferred to another healthcare system and 1 patient who died during the study).
†Based on contingency table analysis and χ^2 test.

tight glycemic control has been seen in other settings as well.[33,48] Still, our results imply that case management interventions could be successfully targeted at the highest-risk patients, improving the efficiency of these interventions dramatically.

This intervention differs substantially in its structure from that of many other case management interventions. The intervention was based on management by a clinical pharmacist rather than a nurse. Although there have been some nonrandomized or short-term studies[34-36] of pharmacists as case managers of diabetic patients, the literature on this is limited. However, pharmacists can play a critical role in the management of patients with chronic diseases, such as congestive heart failure and anticoagulation, that require multiple medications or frequent medication adjustment,[37-39] and we have extended these findings to patients with type 2 diabetes mellitus. Another key difference between this and other management interventions[30] is that this was not a centralized or referral-based program. Rather, the clinical pharmacist was integrated directly into the clinic, where face-to-face contact with patients and providers was possible. In informal discussions, providers indicated that they were satisfied with this type of intervention because there was a level of trust and interaction that they did not perceive in previous centralized disease management investigations. The increased level of trust led to a great deal of autonomy for the clinical pharmacist, who was thus able to function more independently and to make medication adjustments (eg, dosages of insulin or oral hypoglycemic agents) in a more timely manner. In addition, the pharmacist provided direct feedback on diabetes status to patients as a formal communication, and the ability to have informal contact to discuss cases provides an opportunity for collaborative care that is less likely to occur in centralized programs.

There are several limitations to this study. This was a small study involving only 80 patients at a single suburban university-affiliated clinic. The results of the study may not be generalizable to other settings or patient populations. In fact, there is reason to believe that specific aspects of a case management intervention and the patient population are critical factors in whether case management will be effective.[31] In addition, we conducted the study as a quality improvement project aimed at measuring effectiveness in a real-world clinical setting rather than as a strict protocol-driven randomized trial of efficacy. For example, we did not insist on exit measurement of HbA_{1c} levels at a preset time; rather, we obtained results at the time of regularly scheduled follow-up visits and only if the primary providers ordered the appropriate test. This presents some strengths in that the control group represents the underlying patient population more accurately, but it introduced some small differences in duration of follow-up between treatment arms. However, we controlled for differences in duration of follow-up using regression models and still found that the case management intervention was effective. We also do not have information on resource use at present.

Although our intervention was successful, there are issues that need to be addressed on a broader scale before it can be disseminated into general practice. First, a pharmacist is likely to be more costly than a nurse in providing this type of intervention, and clinical pharmacists are often in short supply. However, some of the costs of pharmacist care may be offset by reductions in diabetes complications. Second, this was not a centralized case management system, and disseminating it on a broad scale would generate substantial additional resource requirements. The variance in response to the intervention based on initial HbA_{1c} levels, however, indicates that the intervention may best be targeted to limited patient populations at high risk. Perhaps the best solution would be to integrate a pharmacist case manager into clinics with high-risk patients and to extend the activities of pharmacists who already have clinical duties such as monitoring and adjusting anticoagulation therapy.

This study shows that a pharmacist case manager integrated into a suburban primary care clinic can substantially improve glycemic control and adherence to screening recommendations among high-risk patients with type 2 diabetes mellitus. This offers a somewhat different model of case management than other models that have been tested and one that may offer solutions to some of the concerns (such as fragmentation of care and lack of primary care physician involvement in decision making) that primary care physicians have expressed about current models of centralized care.[49] The differences between various case management strategies need to be more rigorously identified before wide-scale adoption; however, our study offers an effective and efficient approach toward improving conventional diabetes care.

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