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Original Research

Effect of the pharmacist-managed cardiovascular risk reduction services on diabetic retinopathy outcome measures

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Abstract

Background: Diabetic retinopathy (DR) is a progressive, sight-threatening long-term complication of diabetes. Diabetes disease management reduces the risk of developing or progression to a severe form of DR. However, there are no reports of the potential role of pharmacists in DR progression.

Objective: For this study, we performed a retrospective data analysis of patients with diabetes seen at cardiovascular risk reduction services provided by pharmacists with an objective to determine the potential role of pharmacists in the DR progression. These services involve pharmacists working in collaborative drug therapy management (CDTM), using a collaborative practice agreement (CPA) with primary care physicians.

Methods: Patient records and ophthalmological notes were collected for 317 individuals seen by the pharmacists (intervention group) and 320 individuals seen only by a physician (control).

Results: Statistical analysis was performed on 148 individuals in an intervention group and 120 individuals in the control group for which complete records were available. Retinopathy progression remained stable in 89.6 % of individuals in the intervention group compared to 87.9% in the control group. Moreover, the relative risk of retinopathy progressing to a severe form was 1.17 for the control group compared the intervention group.

Conclusions: Our studies provide a proof-of-concept that pharmacists-managed care possesses a potential role in protection from DR, and paves a way for future pharmacists managed care with an emphasis on reducing diabetic complications.

Keywords

Diabetic Retinopathy; Diabetes Mellitus; Pharmacists; Professional Role; Medication Therapy Management; Retrospective Studies; Indiana

INTRODUCTION

The diabetes epidemic is increasing at an alarming rate, with an estimated 30.3 million people, or 9.4% of the US population, having diabetes. With the incidence of diabetes expected to increase to 54.9 million by the year 2030, a precipitous rise in diabetes-associated complications is a major concern.[1] Diabetic retinopathy (DR) is among the most common complications of diabetes and the leading cause of new cases of legal blindness among adults aged 20-74 years in the US. DR is a progressive condition, with nearly all patients with type 1 diabetes (T1D) and > 60% of patients with type 2 diabetes (T2D) develop DR, within 20 years of diabetes.[2] The latest assessment of patients with diabetes suggests a 28.5% estimated prevalence of DR, with a 4.4% prevalence of vision-threatening DR.[3] The vision loss in patients with diabetes occurs through a variety of mechanisms such as retinal detachment, vitreous hemorrhage, macular edema, or capillary non-perfusion. DR is mainly categorized into two stages nonproliferative DR (NPDR) and proliferative DR (PDR). The NPDR is further sub-classified into three stages: mild, moderate and severe NPDR. A meta-analysis study of 27,120 patients reported a pooled incidence of PDR as 11%, and severe vision loss as 7.2% after 4 years.[4,5] Current therapeutic options such as pan-retinal photocoagulation or anti-VEGF work either at the expense of the retina or are only effective in about 35-45% of the population.

The combination of uncontrolled glycemic control and hypertension, failure of timely clinical assessment, and lack of patient awareness are among the greatest risks for vision loss among patients with diabetes.[6-8] Similarly, poor access to care, lack of time, out of pocket expenses, insufficient patient knowledge related to the disease and lack of care/coordination are additional barriers for providing optimal management of DR and its risk factors.[9,10] This leads to an unmet need for developing newer approaches in patients with diabetes to tackle the burgeoning rise in DR.

Primary care physicians (PCP) manage most patients with diabetes, with a recent study suggesting there are 1380 diabetes-related visits to physician offices per 1000 persons aged 65 and over.[11] However, providers of these clinics face significant challenges for providing optimal diabetes care. These include longer time intervals between patient visits,

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limited time during scheduled visits, difficulty scheduling to busy PCP practices, lack of provider awareness of updated diabetes treatment medications, and lack of patient education on diabetes complications.[12,13] The educational, clinical, medication-related, and psychological needs of these patients are complex, and often cannot be addressed during infrequent visits to a PCP.[14,15] Large clinical studies such as the diabetes control and complications trial (DCCT) involving individuals with T1D and UK prospective diabetes study (UKPDS) in patients with T2D revealed tight glycemic, blood pressure, and cholesterol control can substantially reduce risks of microvascular diabetes-related complications. However, the barriers in current healthcare systems make it difficult to achieve the metabolic goals of these patients. There is a requirement of additional resources to overcome deficits in the health care of individuals with diabetes. Many individuals with diabetes fail to receive education about maintaining good glycemic control, medication management, the recommended frequency of tests for better management of diabetes, and information related to the correlation of blood sugar control and prevention of DR.[8,10,16]

Pharmacists are an important pillar of the healthcare system, with evidence supporting joint care with physicians for patients with diabetes. Pharmacist's involvement in medication management, patient education, drug utilization review, and diabetes education have shown significant improvements in HbA1c, LDL-cholesterol, blood pressure, and frequency of adverse drug events.[17-19] Interventions by clinical pharmacists have also led to improvements in medication adherence, patient knowledge, and quality of life. Pharmacist interventions have ultimately lead to dramatic decreases in average medication expenditures per patient and decreased sick days or time away from work.[20-22]

There is a strong association between cardiovascular disease, elevated plasma LDL cholesterol, gross proteinuria, and DR.[23] Long-term maintenance of glycemic control and medication management are some of the greatest challenges faced by individuals with diabetes. However, there are no reports documenting whether the direct intervention by a pharmacist in the management of diabetes and associated micro- and macrovascular outcomes leads to beneficial effects regarding DR progression. To evaluate the potential benefit of pharmacists' interventions on protection from DR progression, a retrospective observational study was completed evaluating retinopathy progression in patients with diabetes managed by pharmacists and physician (intervention group) versus those in routine care (control group). The pharmacists worked in a collaborative drug therapy management (CDTM) service, using a collaborative practice (CPA) agreement with primary care physicians to provide comprehensive cardiovascular risk reduction serviced to patients with diabetes. Pursuant to this agreement, pharmacists in these clinics were able to independently, start, stop, or adjust medications related to diabetes, hypertension and smoking cessation. The pharmacists were also able to provide necessary counseling related to disease-state education, non-pharmacologic management strategies, and additional referrals. Referrals were made by pharmacists to key collaborating providers for patients with diabetes, including ophthalmology, nephrology, neurology, cardiology, podiatry, dentistry and more.

METHODS

Study Design

The study was approved for a database access (#1506049479) of patients with diabetes seen within any clinic of a safety-net healthcare system in downtown Indianapolis, IN, USA. Data were collected from a group of individuals seen by the pharmacist (intervention group; n=317) along with PCP, and individuals only seen by the PCP (control group; n=320). Information from the following categories was collected and entered into Research Electronic Data Capture database (REDCap; https://projectredcap.org/): (a) age, race, and gender, (b) metabolic parameters such as A1C, LDL, HDL, blood pressure, and triglycerides, (c) current medications, and (d) diabetic retinopathy-related information (including ophthalmology appointment dates and retinopathy ratings, as per ophthalmologist's notes). An attending ophthalmologist categorized retinopathy; these notes were used for study purposes. Retinopathy status was graded on the scale of zero to three: no retinopathy (0), mild NPDR (0.5), moderate NPDR (1), severe NPDR (2), and PDR (3). The date of the appointment, the level of retinopathy indicated, and ophthalmologist's name were all recorded under the ophthalmology appointment dates and retinopathy-rating category. (e) The last category was exclusive to the intervention group and included the date(s) of an appointment(s) with the pharmacist.

Statistics

Data analysis was performed on individuals having a record of at least two eye examinations and a complete set of demographic information. The demographic variables such as age, race, and gender were included in the analysis in order to offset any potential sampling bias in the study. A total of 148 individuals in the intervention group and 120 individuals in the control group met this criterion. In both control and intervention groups age was discretized into four categories (<50, 50-69, 70-79, >80) and participants that were included in the study fell into three self-reported race categories (African American, White, and Multiracial). A Chi-squared test and Fisher exact test were conducted to test the Null hypothesis of an equal distribution between the intervention and control groups for the demographic variables of interest. Laboratory assessments of A1c, LDL, and HDL were presented using median and interquartile range and categorized based on the use of insulin therapy. The Mann Whitney U test was performed to test the Null Hypothesis. A p-value of less than 0.05 suggests a significant difference in medians.

Due to the subjectivity of documentation, severity of assessment by different physicians and diversity of physician visits by a respective patient, three different metrics were used to document the progression of DR. For a given patient, the retinopathy progression status was obtained by first taking the difference in retinopathy score on the first and last visit on record and then coded in the following manner: (a) a positive change was coded as 1

(improved), a change of 0 as (0, stable) and a negative change as -1 (worsen). (b) Both positive and zero change were coded as 1 (stable/ improved) and a negative change was coded as – 1 (worsen). (c) Only zero change (coded as 1) and negative change (coded as 0). For metrics (a, b and c), a Chi-squared test was used in order to study whether the proportion of patients whose retinopathy scores remained stable or improved were significantly different in the control and intervention groups. A chi-squared test was also used to assess whether the risk of worsening DR was significantly higher in one of the two groups. In addition to the binary metrics (b) and (c) a logistic regression analysis was conducted to model the odds of retinopathy worsening in the control group versus and intervention groups. The response variable in the logistic regression model was the binary condition of the patient retinopathy (improve/worsen) and the factor of interest was the indicator variable representing whether the patient belongs to the intervention or control group. Comparison between the control and intervention groups were performed using a likelihood ratio test. The demographic variables gender, race, and age were also added to the model as a covariate to adjust for their effect. We performed a power analysis for comparing the odds of retinopathy worsening in the control and intervention groups for the logistic regression model assuming a moderate effect size. The true but unknown effect size (odds ratio) was assumed to range between 1.2 and 1.5. This would suggest that the intervention group 1.2 to 1.5 times less likely will experience retinopathy than the control group. The power analysis was computed using Shieh-O'Brien large sample approximation.[24,25] Based on this power analysis the required sample size ranges from 899 to 2202 patients in each group depending on the unknown true effect size (odds ratio) and unknown true probability of retinopathy worsening in the two groups. The sample size was estimated at a power of 0.8 and 0.05 level of significance.

In order to further examine the effect of pharmacist's intervention on the progression of DR, patients in the intervention groups were divided into three categories based on the total number of pharmacist visits on record. These categories are 0-5 visits 6-20 visits and >20 visits. The percentage of cases for which retinopathy worsen in each of these three categories was then compared. All analyses were implemented using Statistical Analysis Software (version 9.4, SAS Institute Inc., Cary, 115 NC)

RESULTS

There was no significant difference in distribution in the demographic variables (gender, race, and age) between the control and intervention group (Table 1). This suggests that the control and intervention group used were comparable for further analysis. The intervention group had marginally higher HbA1c, LDL and lower HDL cholesterol with a statistically insignificant difference. Patients in the intervention group were followed on average for 1.77 years with a median duration of a follow-up time of 1.25 years while patients in the control group were followed on average 1.55 years with a median duration of follow up of 1.19 years (Table 1). Patients in the intervention group had marginally more ophthalmology visits than patients in the control group with an average number of visits of 3.32 and 2.27 respectively over the time duration patients were followed (Table 1).

In the intervention group using metrics (c), retinopathy remained stable as compared to a control group. In

Table 1. Baseline characteristics of Pharmacist intervention group and control group

	Intervention (n=148)		Control (n=120)				
Demographic variables	**n**	**%**	**n**	**%**	**Chi-sq (df)**	**p-value**	**Fisher Exact test p-value**
Gender					1.80 (1)	0.179	0.210
Male	65	43.92	43	35.83			
Female	83	56.08	77	64.17			
Race					2.93 (2)	0.230	0.245
Black/African American	99	66.89	75	62.50			
White	43	29.05	34	28.33			
Multiracial	6	4.05	11	9.17			
Age					5.15 (3)	0.160	0.161
< 50	20	13.51	19	15.83			
50-59	48	32.43	27	22.50			
60-69	54	36.49	42	35.00			
>70	26	17.57	32	26.67			
Lab results	**Median**	**IQR**	**Median**	**IQR**	**p-value****		
A1c							
Insulin	8.4	2.6	8.1	2.3	0.241		
Non_insulin	7.1	2.8	7.1	1.9	0.932		
HDL							
Insulin	42	18	45	17	0.098		
Non_insulin	46	20	46	18	0.918		
LDL							
Insulin	96	50	88	56	0.191		
Non_insulin	95	66	98.5	40	0.904		
	Mean (median)	**Min (max)**	**Mean (median)**	**Min (max)**			
Duration of Time (years) patients were followed	1.77 (1.25)	3 days (6.55)	1.55 (1.19)	12 days (5.25)			
Number of Ophthalmology visits	3.32 (3)	2 (20)	2.27 (2)	2 (5)			

Table 2. Effect of Pharmacist intervention on Diabetics Retinopathy

	Intervention		Control				
Demographic variables	**n**	**%**	**n**	**%**	**Chi-sq (df)****	**p-value**	**Fisher Exact test p-value**
a-Retinopathy Progress status					0.350 (2)	0.839	0.837
worsen	13	8.78	12	10.00			
stable	112	75.68	87	72.50			
Improved	23	15.54	21	17.50			
b-Retinopathy Progress Binary					0.115(1)	0.733	0.833
worsen	13	8.78	12	10.00			
stable/Improved	135	91.21	108	90.00			
c-Retinopathy Progress Binary					0.165 (1)	0.684	0.831
worsen	13	10.4	12	12.12			
stable	112	89.6	87	87.87			

Number of pharmacist visits for the Intervention Group	**[0-5]**		**[6-20]**		**[21-60]**	
	n	**%**	**n**	**%**	**n**	**%**
Stable/ Improved	25	92.59	60	85.71	38	79.17
Worsen	2	7.41	10	14.29	10	20.83

addition, there was a decrease in the percentage of patients who progressed to a severe form of DR in the intervention group as compared to control. For metrics (a) and (b) no significant difference was found between the control and intervention groups (Table 2). This corresponds to a relative risk of retinopathy worsening in the control group as 1.17 when compared to the intervention group. After adjusting for the effect of the demographic variables, the odds ratio of retinopathy progressing to a severe form in the control group was 1.31 (95%CI, 0.5 to 3.05) (Table 3).

In order to further examine the effect of pharmacist's intervention on the progression of DR, a comparison was made with DR progression and the number of visits with pharmacists. A higher percentage of patients were classified as having stable DR if they had visited a pharmacist between 0-5 times (95.59%) versus those that visited pharmacists between 6-20 times (85.71%). Also, a lower percentage of patients were classified as stable DR if they visited pharmacists more than 20 times (79.17%) than between 6-20 times (Table 2).

DISCUSSION

Diabetes management programs play an integral role in the management of patients with diabetes.[26] It has been shown that multidisciplinary team care by a PCP, advanced practice nurse and clinical pharmacist leads to significant improvements in glycemic control.[27] Our study further demonstrates that in individuals, which received pharmacists-managed care, remained either stable or improved on retinopathy scale, also the absolute risk of worsening the retinopathy grading reduced in an intervention group. This would roughly lead to 100,000 more cases of stable or improved DR considering 1.2% ARR in our study and taking into account 28.5% prevalence of DR in 30.3 million diabetics in the United States.

A disease management program involving a pharmacist has reported a 0.8% decrease in A1c in 12 months.[28] In our study, the glycated hemoglobin levels between two patient groups differed insignificantly at the baseline. The HbA1c reports were not available at study termination; therefore, we cannot concur that glycemic control indeed helped in protection from DR. However, the unpublished data from our practice site has shown sustained A1c reductions of 1-2% by pharmacist-managed patients for at least 4 years suggest that there may be a similar A1c reduction in our study participants.

This study is among the first of its kind showing a potential role of pharmacists-involvement in diabetes care leading to a reduction in DR progression. While the effect is modest, the concept is quite compelling due to the continued expansion of privileges for pharmacists on a state and national level. This proof of concept of pharmacists role in slowing the progression of DR comes in addition to all previously documented benefits pharmacists can have on glycemic control, medication adherence, healthcare costs, and others. Similarly, community pharmacists are uniquely placed among healthcare individuals and often serve as the first-line of entry into the healthcare system for many patients. With many of these pharmacists expanding roles to include disease education and medication therapy management, there is an increased opportunity for pharmacists to have a significant effect on this important diabetes outcome.

Our results support the hypothesis that inclusion of a pharmacist with an ability to provide direct patient care as part of an interdisciplinary team managing diabetes can lead to less progression of DR. While the specific reason for the lack of DR progression was not determined in our study, there is a direct correlation between improvements in glycemic control and worsening of DR. Exposure to direct care by pharmacists did lead to significant improvements in glycemic control compared to the control group. While the number of ophthalmology referrals was not tracked, the

Table 3. Logistic Regression Results for Comparing the Odds of worsening diabetic retinopathy in Control and Pharmacist Intervention Groups

n_o / total n_o (%)	**Worsening of diabetic retinopathy**	**Adjusted Odds Ratio[ǂ] (95%CI)**	**p-value[ɬ]**
Control	12/ 99 (12.12)	1.31 (0.56-- 3.05)	0.534
Intervention	13/125 (10.40)		

ǂ Adjusted Odds Ratio was obtained using a logistic regression modeling of the odds of retinopathy worsening in patients in the control and interventions groups. The logistic regression was adjusted for the effect of the demographic variables age, gender and race.
ɬ Maximum likelihood test was utilized to generate the p values for comparing the odds of retinopathy worsening in the control and intervention groups.

pharmacist providing direct care to the patients could provide this service and are in a position to help support this important aspect of diabetes care (i.e. serving as another healthcare provider to ensure patients with diabetes received appropriate ophthalmology care).

While this study did not involve community pharmacists, pharmacists working in those settings can assume many roles that mirror what the pharmacist in this study was able to do. Data support the role of community pharmacists in improving glycemic control and they could also serve as an additional healthcare provider monitoring for, and reminding patients about, appropriate ophthalmologic care for their diabetes.[19] Pharmacist in the community also remove, or mitigate, a risk cited for patients with DR. This includes the necessity of having a prior appointment, and potential long wait times just to discuss patient concerns. Pharmacists can also be uniquely positioned to provide education about eye complications related to diabetes and provide screening for ophthalmology appointments of their patients. This supports previous studies suggesting early referral to an ophthalmologist can lead to as much as a 50% reduction in the risk of severe visual loss and vitrectomy.[6,29,30]

With highlighting benefits of pharmacist's intervention on retinopathy progression, the following limitations were perceived; (i) While the baseline demographics of patients included in this study did not differ significantly, retrospective data collection only provided baseline glycemic control of these patients, (Table 1). It would be interesting in future studies to correlate the progression of DR with a degree of glycemic control over time. (ii) Another difficulty of this retrospective analysis was getting accurate retinopathy ratings. (iii) This study involved individuals that received pharmacist's intervention related to a cardiovascular risk reduction, the patients were not educated on eye complications, vision problems.

CONCLUSIONS

Our study provided a proof-of-concept that involving a pharmacist in the progressive care of patients with diabetes can help in both reducing severity of DR and achieving satiety for DR progression. Future studies aimed specifically at educating patients about eye complications and timely reminders at prescription refill may help in reducing the risk of DR in individuals with diabetes.

CONFLICT OF INTEREST

None of the authors have affiliations with or involvement in any organization or entity with a financial interest in the subject matter or material discussed in this manuscript.

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