Long-Term Effect on HbA1c in Poorly Controlled Diabetic Patients Following Nonmydriatic Retinal Image Review at the Time of Endocrinology Visit

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Abstract

Background: Patient education demonstrates variable benefits on diabetes control.

Introduction: To examine the effect of discussing nonmydriatic retinal imaging findings during a single endocrinology visit on HbA1c levels after 6, 12, and 60 months.

Materials and Methods: Patients with HbA1c >8.0% and diabetic retinopathy were previously recruited for a prospective study looking at the change in HbA1c at 3 months between those assigned to a session of nonmydriatic imaging with discussion of retinal findings and those assigned to routine endocrinology evaluation alone. The patients were subsequently evaluated at 6, 12, and 60 months after the initial intervention.

Results: Fifty-three of the 57 originally recruited intervention subjects (93%) and 48 of 54 subjects in the original control group (89%) were evaluated at 6 and 12 months and 44 patients in each group (75% and 81%, respectively) at 60 months. At 6 months, the intervention group maintained larger decreases in median HbA1c compared to control (−1.1 vs. −0.3, respectively, $p=0.002$) with a trend persisting at 12 months (−0.6 vs. −0.2, respectively, $p=0.07$). After 60 months, there was no significant difference in the median change in HbA1c between treatment and control groups (0.3 vs. 0.1, respectively, $p=0.54$).

Discussion: The short-term improvement in HbA1c resulting from discussion of retinal findings persists throughout the first year in this diabetic cohort, but its magnitude declines with time and becomes statistically insignificant at some point between 6 and 12 months.

Conclusions: In patients with poorly controlled diabetes, retinal imaging review may help improve glycemic control but may require repetition periodically for benefit beyond 6 months.

Keywords: diabetic retinopathy, nonmydriatic retinal imaging, glycemic control, telemedicine

Introduction

Optimizing blood glucose control is fundamental to reducing complications associated with diabetes. Educational efforts have demonstrated variable benefit on subsequent glycemic control as measured by HbA1c.^{1,2} We previously demonstrated a positive effect on short-term (3-months) glycemic control using a noninvasive imaging intervention that educates patients about their retinopathy findings during their endocrinology visit.³ In this study, we report the longer-term follow-up of glycemic control at 6, 12, and 60 months following this single original education session.

Materials and Methods

The study protocol was approved by the Institutional Review Board of the American University of Beirut Medical Center (AUBMC) and was in accordance with the Helsinki declaration. Written informed consent was obtained for all subjects. This study was registered at the ANCTR website with trial registration number ANCTR126 09000362291. This trial invited the original 111 subjects from the initial prospective study and measured HbA1c level at the AUBMC laboratory 6, 12, and 60 months after the initial intervention.

The “intervention” has been described previously.³ Briefly, among a cohort of 111 subjects with poorly controlled diabetes and documented retinopathy, a randomized group of 57

received nonmydriatic retinal imaging performed by a single technician during their endocrinologist evaluation, followed by viewing of their own images and a brief discussion of the findings by a single retina specialist (H.S.). The retina specialist showed the subjects their images on a computer monitor highlighting clinical findings. Discussion explicitly included the following: (1) presentation demonstrating a range of diabetic retinopathy (DR), including a normal fundus, mild-moderate nonproliferative DR, active proliferative DR, and tractional retinal detachment (*Fig. 1*); (2) a brief summary of the results of the Diabetes Control and Complications Trial⁴ and the United Kingdom Prospective Diabetes Study⁵ regarding HbA1c control and DR; and (3) emphasis on the importance of blood glucose control to delay onset or slow progression of DR. The rest of the patients had their standard conventional endocrinology evaluation without the added personalized session.

As previously reported, 3 months after the endocrinologist visit, HbA1c measurement was performed for each subject and shown to be significantly lower in the intervention group.³ In the current study, we report the HbA1c data in these subjects 6, 12, and 60 months after the single original intervention. All

blood tests were performed at the same laboratory using the same technique throughout the duration of the study (VAR- IANT^{TM}II and D-10 Hemoglobin Testing Systems by Bio-Rad using high performance liquid chromatography).

STATISTICAL ANALYSIS

Statistical analysis was performed using SAS software v.9.4 (SAS Institute, Inc., Cary, NC). Changes in HbA1c were calculated after 6, 12, and 60 months and compared across treatment and control groups using a Wilcoxon signed-rank test. The baseline HbA1c level was the preintervention measured HbA1c. We also use logistic regression to model the relationship between the intervention and the change in HbA1c while controlling for baseline HbA1c. $p < 0.05$ was considered statistically significant.

Results

Of the 57 original intervention subjects, 53 (93%) received repeat HbA1c evaluation at 6 and 12 months and 44 (77%) at 60 months. From the original control group of 54 patients, 48 (89%) received repeat HbA1c at 6 and 12 months and 44 (81%) at 60 months (*Fig. 2*). *Table 1* shows baseline characteristics of

Fig. 1. Images presented at the time of the intervention demonstrating the full spectrum of diabetic retinopathy. Color images are available online.

Fig. 2. Follow-up flow diagram.

the follow-up cohort. There were no significant differences between the intervention and control subjects at any follow-up period. Furthermore, there were no substantial differences in clinical or sociodemographic characteristics between the follow-up and original cohorts.³

HbA1c was reduced to a greater extent in the intervention group than in the control group (Fig. 3) at 3 months (median change -1.4 vs. $+0.2$, $p=0.001$), 6 months (-1.1 vs. -0.3 , $p=0.002$), and 12 months (-0.6 vs. -0.2 , $p=0.07$). The magnitude of benefit was greatest at 3 months following intervention and decreased steadily at the 6- and 12-month follow-up visits. After 60 months, the HbA1c was no longer improved from baseline (median change 0.3 vs. 0.1) and was also not statistically different between intervention and control ($p=0.54$). The benefit of the intervention on HbA1c

reduction remained statistically significant at 6 months even when controlling baseline HbA1c.

Discussion

Vision loss from DR remains a major cause of visual impairment in the working-age population in most developed countries. It is well established that glycemic control can markedly reduce the development and progression of DR.^{3,5} In addition, studies have demonstrated that vision loss is one of the most feared of all complications from diabetes.^{6,7} We demonstrated previously the significant effect of a single intervention at the time of endocrinology evaluation using a subject's own retinal fundus images and brief retinopathy education for improving diabetes control as measured by subsequent HbA1c at 3 months.¹ In this study, we were able to reexamine HbA1c in $\sim 93\%$ of the original cohort at 6 and 12 months and $\sim 80\%$ of the cohort after 60 months. Interestingly, despite no additional intervention, these data demonstrate a continued HbA1c benefit at 6 months and a trend suggesting persistence at 12 months after the original intervention session.

The magnitude of HbA1c reduction diminished consistently with longer duration of follow-up. After 60 months

of follow-up, the intervention effect was no longer statistically significant and the mean HbA1c returned to similar levels than at study entry. These data suggest that further reinforcement with subsequent interventions may be needed at yearly intervals, although it remains unknown how effective subsequent interventions would be compared to the original effort.

The fact that a single intervention could have such long-lasting effects is surprising. Several aspects of the interventional approach and the particular subject cohort may account for this. It is well established that vision loss ranks among the greatest fears in patient populations, sometimes feared even more than death.^{6,7} The intervention in this study directly presented the range of retinal pathology that can occur from DR and then compared that to the current

Table 1. Baseline characteristics

	AT 6 AND 12 MONTHS		AT 60 MONTHS	
	INTERVENTION GROUP (n=53)	CONTROL GROUP (n=48)	INTERVENTION GROUP (n=44)	CONTROL GROUP (n=44)
Age (years), mean $\pm$ SD	54.5	55.5	53.8	54.6
Female (%)	59.6	64.5	58.1	65.9
Diabetes duration (years), mean $\pm$ SD	9.3	9.9	9.0	9.8
Hypertension (%)	55.8	60.4	58.1	56.8
Insulin use (%)	36.5	43.8	37.2	43.2
Initial HbA1c, mean $\pm$ SD	10.2	9.9	10.1	10.0

All *p*-values >0.05.

SD, standard deviation.

image of the subject themselves. Ways to minimize potential vision loss were then discussed, including the optimization of glycemic control.

Nonmydriatic digital imaging technology allows retinal image acquisition at the time of a patient's endocrinologist visit to be feasible, repeatable, and accurate.⁸ This imaging is also well tolerated⁹ since, unlike traditional dilated fundus examinations, it is less time consuming and avoids pupillary dilation,¹⁰ and vision recovers rapidly after the nonmydriatic imaging.¹¹ Thus, in this study, subjects could view their own images immediately and see the pathological changes occurring in their own eyes. Combined with similar images of the severe complications that retinopathy can cause, this

approach may have helped personalize both the experience and the risks, thus possibly providing additional impetus for subsequent efforts to improve glycemic control.

This cohort is also unique compared to other interventional studies in that it is derived solely from an endocrinology clinic in Beirut. It is thus unlikely that the patients had seen prior images of their retina, and thus, the impact of seeing their own pathology for the first time might be particularly powerful. Furthermore, the cohort's baseline mean HbA1c was $\sim$ 10.0, a high value suggesting substantive risk of retinopathy progression and eventual vision loss if not appropriately addressed. This may have further increased

impact of the intervention. In addition, vision loss in less developed countries often has an even greater personal and family burden than in developed societies given a relative lack of supportive services and expendable income. Finally, the physician subject interaction may be particularly strong in this cohort as evidenced by the excellent long-term follow-up.

The intervention benefits consistently diminished over time becoming statistically insignificant at some point between 6 and 12 months. These data suggest that further reinforcement with subsequent similar interventions may be needed at yearly intervals. However, it remains unknown whether repeating the same intervention would provide similar motivation and benefit over time. In addition, it should be noted that this imaging approach does not replace a comprehensive retinal ophthalmologic examination that is generally recommended at least annually for patients with diabetes when such resources are available. Whether continued encouragement to maintain recommended ophthalmological follow-up or the receipt of such ophthalmic care would modify the observed HbA1c response is also unknown. Changes in DR severity were not evaluated in this study due to the inadequate subject number at any given DR severity level. Furthermore, this study did not evaluate specific behaviors that may have been modified by this intervention, nor whether these behaviors could be encouraged or prolonged.

A previous study by the Diabetic Retinopathy Clinical Research Network (DRCR.net Protocol M) evaluated a scripted educational intervention at 4-month and yearly intervals.¹² The intervention group did not have any HbA1c

Fig. 3. Follow-up flow diagram. Color images are available online.

Table 2. Comparison of Baseline Characteristics of the 12-Months Cohort with Diabetic Retinopathy Clinical Research Network Protocol M

	CURRENT STUDY INTERVENTION	CURRENT STUDY CONTROL	PROTOCOL M FREQUENT INTERVENTION	PROTOCOL M ANNUAL INTERVENTION	PROTOCOL M FREQUENT CONTROL	PROTOCOL M ANNUAL CONTROL
Age (years), mean	55	56	65	63	64	61
Female (%)	60	65	55	58	50	58
Diabetes mellitus type I (%)	10	15	11	13	12	12
Diabetes duration (years), median	9	10	17	14	18	13
Hypertension (%)	56	60	63	58	63	57
Insulin use (%)	37	44	83	77	81	74
Initial HbA1c, mean	10.2	9.9	8.6	8.4	8.3	8.3

All *p*-values >0.05.

benefit. In DRCR.net Protocol M, the intervention occurred at the ophthalmologist office and involved providing the subject with their HbA1c, DR severity, brief educational discussion, and a brief knowledge assessment. Protocol M did not use the subjects own images, was performed entirely within the United States, and was not focused on underserved localities. Furthermore, as shown in *Table 2*, there were substantial differences in cohort characteristic between Protocol M and the current study.

Compared to Protocol M, the current study has younger subjects, higher percentage of women, shorter duration of diabetes, less hypertension, less insulin use, and higher HbA1c. Thus, it appears that the DRCR subjects may have required less intense intervention and were more aggressively treated at baseline, with less room for HbA1c improvement. Furthermore, Protocol M intervention was performed in an ophthalmology office setting, suggesting that those subjects may have had greater prior education and awareness of retinopathy. Protocol M also did not include direct review of the subjects' own retinal images.

In conclusion, for this particular cohort of diabetic patients, a single, focused, personalized retinopathy education and retinal imaging session during an endocrinology visit resulted in sustained improvement of HbA1c for up to 6 months. However, the benefit declined with time and was no longer evident after 5 years. Nevertheless, given that substantial reductions in ocular and other medical complications are closely associated with improvement of HbA1c, further exploration is warranted to

determine why this approach proved beneficial over this period and how to successfully extrapolate such interventions to other cohorts.

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No competing financial interests exist.

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