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EUGLYCEMIC PROGRESSION: WORSENING OF DIABETIC RETINOPATHY IN POORLY CONTROLLED TYPE 2 DIABETES IN MINORITIES

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Abstract

Aims—In type 2 diabetes, early effects of strict near-normalization of glucose control on macrovascular and microvascular disease are still uncertain. We evaluated the effects of early dramatic improvement in glycemia on retinal disease in poorly controlled diabetes.

Methods—A retrospective, case-control study in public hospital patients with type 2 diabetes, who had annual retinal imaging as part of a case management program or standard diabetes care. Patients included had ≥2 two retinal images ≥1 one year apart, and at least 3 HbA1C measurements. Retinal images were graded using a modified Scottish Diabetic Retinopathy grading scheme. An 'intensive' group (n=34) with HbA1C decrease >1.5% was compared with randomly chosen patients (n=34) with minimal HbA1C changes.

Results—Mean HbA1C (±SEM) over two years was similar in intensive (8.5±0.21%) and control groups (8.1±0.28%, p=NS). However, the intensive group had higher baseline HbA1C and a mean maximal decrease of 4.0±0.41% in contrast to the control group (0.2±0.11%). Retinopathy grade progressed +0.7±0.25 units from baseline in the intensive group (p = 0.015), a 22.6% worsening. The control group changed minimally from baseline (0.03±0.14 units, p=NS). Change in retinopathy grade was significantly different between groups (p=0.02). More eyes worsened by ≥1 retinal grade (p=0.0025) and developed sight-threatening retinopathy (p=0.003) in the intensive group. Visual acuity was unchanged.

Conclusions—Diabetic retinopathy significantly worsened in poorly controlled type 2 diabetes after early intensification of glycemic control and dramatic HbA1C change. Retinal status should be part of risk-factor evaluation in patients likely to experience marked reductions in HbA1C in poorly controlled diabetes.

Keywords

Diabetic Retinopathy; intensified glycemic control; case management; euglycemia; minority populations

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Excellent glycemic control is a major clinical target for patients with diabetes since the first unequivocal evidence for its efficacy in delaying and preventing microvascular disease (1,2). Recommendations for improving glycemic control are based on evidence of its beneficial effect, limited only by the risks of hypoglycemia, which are increased with tight glycemic control (3). Evidence to the contrary, i.e., that introducing tight glycemic control may also have deleterious effects, was also recognized in early trials, and evidence suggested this was a transient phenomenon (4). An initial deterioration in retinal findings during intensive therapy in the Diabetes Control and Complications Trial (DCCT) was observed in Type 1 patients with pre-existing retinopathy, but this improved if tight glycemic control was maintained over time (4).

Less is known about the possible deleterious effect of the induction of tight glycemic control in type 2 diabetes; especially with respect to the effect of rapid lowering of HbA1C. Retinopathy may progress (5) and a recent report indicated that patients with pre-existing cardiovascular disease (CVD)may respond poorly to the imposition of tight glycemic control (6). The ACCORD study of type 2 diabetic patients with, or at-risk for, CVD was halted prematurely in response to increased cardiac mortality associated with near-normalization of HbA1C (6,7). Thus, accumulating data support the contention that some patients with type 1 and type 2 diabetes are potentially at risk for worsening of diabetes complications when intensive glycemic control is initiated (8).

This phenomenon may be of particular concern in patients with poor glycemic control in whom large changes in HbA1C can occur during induction of tight control regimens, even if target values are not achieved. This setting is common in minority and indigent populations with poor access to medical care, where elevated HbA1C levels are common and micro and/or macro vascular complications of diabetes in patients with long-standing disease is frequently observed (9,10). The feasibility of initiating and maintaining glycemic control in these populations has been demonstrated (11-13), raising the possibility that these patients may be at risk for an initial ‘euglycemic progression’ of complications when rapid and substantial improvement in glycemic control is successful. We tested this hypothesis in a group of predominantly minority patients with poor control entered into a successful case management program (11,12) in a public hospital setting.

RESEARCH DESIGN AND METHODS

This is a retrospective study of retinal images in patients who participate in the Diabetes Program at Harbor-UCLA Medical Center. All patients with diabetes are offered annual retinal screening using photography, as part of their standard diabetes management. In addition, many of these patients are offered access to a Diabetes Case Management Program designed to assist patients in achieving their glycemic and other management goals (11,12).Subjects for this study were patients who participated in the Diabetes Program and who had retinal images during the period studied, and many of whom participated in the Case Management Program as well. This project was part of a protocol approved by the Institutional Review Board at the LA Biomedical Research Institute.

Inclusion and Exclusion Criteria

Patients were included in the study if they fulfilled the following criteria: 1) diagnosis of type 2 diabetes, 2) age of at least 18 years, 3) documentation of at least two sets of retinal images at least one year apart, 4) measurement of HbA1C at the time of each set of retinal images (±3 months) and 5) documentation of at least one additional HbA1C measurement between the first and last retinal images. Exclusion criteria included 1) diagnosis of type 1 diabetes, 2) lack of at least two sets of retinal images, 3) lack of HbA1C close to either set of

images and/or one between, 4) patient follow-up of less than one year. Patients with bilateral ungradeable retinal images were also excluded from this study.

Study Design

We selected patients from our Case Management Program who met criteria for the study based on available image sets, presence of corresponding HbA1C measurements and minimum length of follow-up. In addition, we required that patients either achieve HbA1C ≤7.5% or demonstrate a decrement >1.5% in HbA1C levels in response to case management. This group was called the intensive therapy group; thirty-four patients fulfilled entrance criteria as well as the additional criterion for improved glycemic control.

A control group was derived from patients in our standard Diabetes Program who had been referred for retinal imaging between September 2005 and August 2007. We reviewed the records of 1,106 patients who had retinal images in order to find 34 controls that met the entrance criteria listed above as well as an additional criterion that limited the maximum HbA1C decrement between images to <1.5%. This was designed to limit overlap between the intervention and control groups.

We also obtained information regarding blood pressure, serum creatinine, and serum lipids. The lipid panel consisted of total serum cholesterol, LDL cholesterol, HDL cholesterol and triglycerides obtained after a 10 hour fast. The data was obtained within a 3-month window before or after the baseline retinal image and again around the time of the second set of retinal images.

Retinal Imaging

All patients included in this study had at least two sets of retinal images. These are single-field images that capture the disc and the area of the retina lateral to it, including the macula. Bilateral images were obtained using a 45 degree Canon non-mydriatic digital retinal camera (Canon CR6-45NM, Japan). Four patients (of a total of 68 patients in both groups) had images obtained using a Polaroid retinal camera (Canon CR4-45NM). All images were obtained under dilated conditions. Each image was analyzed and graded in a blinded fashion by an independent reader using a modified Scottish Diabetic Retinopathy Grading Scheme (14,15). The grading scale was quantified using units assigned to each eye based on level of retinal disease present, as follows: no detectable retinopathy—1 unit; minimal retinopathy—2 units; moderate retinopathy—3 units; severe retinopathy—4 units; proliferative retinopathy or clinically significant macular edema–5 units. A maximum of 5 units could be assigned per eye and each eye was assigned a grade dependent on the highest scoring pathology present in that eye. The assigned grade for each eye was combined to provide a composite score with a maximum of 10 units. The independent reader was unaware of any identifying information pertaining to each set of images and was also unaware of assignment to intensive or standard-control groups.

HbA1C measurement

HbA1C was measured using high-pressure liquid chromatography (non-diabetic reference range 4.2-5.8%, using methodology traceable to the DCCT (Tosoh Bioscience, Tessenderlo, Belgium). In each case, the HbA1C corresponding to the retinal image was obtained within a three month window before or after each image. At least one other HbA1C measurement, obtained between the first and last, was required to calculate maximal reduction in HbA1C and to provide the third measurement that enabled average HbA1C to be calculated for the period studied. In each patient, the lowest HbA1C was chosen as the interim measurement when more than one intermediate sample was available.

Statistical analysis

This study was designed to compare changes in severity of diabetic retinopathy over time in the intensive group versus the control group. The primary study outcome was change in grade of diabetic retinopathy between two sets of retinal images; each eye being graded separately, but reported as a composite score for both eyes. Duration of follow-up was defined as the time between retinal imaging. Statistical analysis was performed using the NCSS package (Kaysville, Utah). Paired or unpaired Student t Tests were used to compare the two groups, as appropriate for within and between group comparisons. Categorical variables were analyzed using the Chi Square statistic. Statistical significance was set at $p<0.05$. Data are presented as mean ± SEM.

RESULTS

Characteristics of study participants

The baseline characteristics of the study participants are shown in Table 1 for both the intensive (n=34) and control groups (n=34). Mean age was similar in both groups, about 52 years. Women were 43% of the intensive group and 50% of the control group. Ethnicity was heavily minority. Twenty three patients were on insulin in the intensive group and 18 in the control group. Twenty five patients had diagnosed hypertension in the intensive group and 22 amongst controls. Duration of diabetes prior to the study was shorter in the intensive group, 8.4± 1.12 years versus 13.1± 1.52 years in the control group (p=0.017). Baseline HbA1C was higher in the intensive group, 10.7± 0.35%; and 7.8 ± 0.27% in the control group (p<0.001) (Table 2).

Baseline serum creatinine, total, LDL, HDL cholesterol and triglycerides were similar in each group at baseline (Table 1) and also at the time of the second set of retinal images (data not shown).

Response of HbA1C to Diabetes Management

Duration of follow-up (time between retinal images) was similar, about 25 months in each group (Table 2). In the intensive group, a marked decrease in HbA1C took place over the first year of management, with the mean nadir at about 13 months (Table 2). The decrement in HbA1C was 4.0 ± 0.41%, resulting in a final HbA1C of 6.7± 0.35%. In contrast, HbA1C in the control group was essentially unchanged, with a decrement of only 0.2± 0.11%. The average HbA1C, despite the difference in the baseline values, was similar in each group when averaged over the duration of the study: 8.5± 0.21% and 8.1± 0.28% (p=0.30), in the intensive and control groups respectively (Table 2). Thus, on average, the patients in each group were exposed to similar degrees of glycemic control over the duration of the study; the change in HbA1C was the primary distinguishing feature between the two groups with respect to glycemic control.

Retinal Grading

A total of 64 eyes were gradeable in the intensive group and 65 eyes in the control group (out of a maximum of 68 eyes in each group).At baseline, retinopathy was slightly, but not significantly worse in the control group, 3.9± 0.43 versus 3.1± grading units in the intensive group (p=0.12, Table 2), attributable to the longer duration of diabetes in the controls. Over approximately 25 months of follow-up in each group, the retinopathy grade changed little in the control group (0.03 ± 0.14 units, p=NS). In the intensive group, retinopathy grade changed by almost 23%, with significant worsening of 0.7± 0.25 units(p=0.015) compared with baseline. This change in retinopathy grade in the intensive group was also significantly different when compared with the change that occurred in the control group(p=0.02).

The overall change in retinopathy grade was associated with at least one step progression in 25 eyes of a total of 64 gradeable eyes evaluated in the intensive group (39% of eyes evaluated). In the control group only 10 eyes (15%) demonstrated at least one step progression out of a total of 65 gradeable eyes evaluated, significantly less than the intensive group, (p=0.0025). Despite the overall worsening in retinopathy grade found in the intensive group, few eyes progressed to sight-threatening retinopathy (change to Grades 4 or 5 from Grade 3 or less) in either group, though the difference was significant (8 eyes in the intensive group versus 0 eyes in the controls, p=0.003). There were no significant changes in visual acuity in either group (data not shown).

Role of Baseline Glycemia on Progression of Retinopathy

Because worsening retinopathy in the intensive group could be attributed to poor initial glycemic control in that group, we also examined a subset of patients in the control group with the worst glycemic control. All control group patients with starting HbA1C ≥9% were evaluated (n=10). This sub-group had similar characteristics to the overall control group with little change in HbA1c during the study: starting, ending and average HbA1c were 9.7± 0.18, 9.8±0.33 and 9.9±0.36%, respectively. Prior diabetes duration was lengthy, 13.9 ± 3 years, and duration of follow-up in the study (23.7±4.9 months) was similar to the intensive group and the entire control group. Initial retinal scoring for the sub-group was 3.7±0.79 units, similar to the entire control group. Little change took place in retinal scores over the duration of the study in this poorly controlled subgroup, 0.1±0.28 units (significantly different from the change in retinal score in the intensive group, p=0.018). Thus, elevated HbA1C that remained unchanged was not associated with progression of retinopathy in this study. This suggests that initial poor glycemic control may be necessary but insufficient for retinopathy progression; a large improvement in HbA1C is likely a key contributor.

CONCLUSIONS

This study demonstrates that large reductions of A1C in poorly controlled type 2 diabetes in a predominantly minority population is associated with worsening of diabetic retinopathy. Although tight glycemic control has long been a primary goal of diabetes management (1-3),there were early warnings that in some patients rapid improvement might have deleterious effects (1,4). In type 1 diabetes, initial worsening was observed in the secondary prevention arm of the DCCT (4), but in type 2 diabetes, there are no similar large scale studies with data on pre-existing retinopathy. The United Kingdom Prospective Diabetes Study (UKPDS), was a primary prevention trial, so that patients had newly diagnosed diabetes with little or no pre-existing retinopathy and worsening was not described (2).To our knowledge, only one study, in which patients were switched to insulin treatment showed worsening of diabetic retinopathy in type 2 diabetes (5).

A feature common to studies demonstrating progression of retinopathy is that patients in worse diabetes control are at highest risk after intensification of glycemic control (4,5). In recent years we have developed methods using case management as a tool for improving glycemia in patients in a public hospital setting, where HbA1C concentrations are often very elevated (11,12). Since successful intervention in such patients might put them at risk for worsening of retinopathy, the data on patients in our case management cohort enabled us to test this hypothesis in a group of predominantly minority patients, known to be at higher risk for retinopathy (10), and who, as exemplified in the intensive group in this study, had remarkable improvement in glycemic control, with average HbA1C reduction of 4%. This dramatic improvement provided an opportunity to test its role in worsening retinopathy; in the previous study of type 2 diabetes (5), average reduction in mean HbA1C levels was 2.2%.

After initiation of case management, the intensive group, who by design had the most dramatic response in HbA1C reduction, experienced significant deterioration in diabetic retinopathy grades. This deterioration occurred despite factors that should have acted to make the two groups have a similar retinopathy course: same study duration (a mean of about two years) and similar overall glycemic control (average HbA1C concentrations over the course of the study). Furthermore, worsening retinopathy in the intervention group occurred despite two important mitigating factors at baseline: shorter diabetes duration and a lower mean retinopathy grade, both of which are potentially protective. Thus, the deterioration in the intensive group suggests that initial poor glycemic control paired with rapid HbA1C reduction is a powerful influence on retinopathy progression, with greater effect in this study than prior duration of diabetes.

These findings are in contrast to the results of our previous study of case management and glycemic control in the same patient population, using the same case management methods (12). In that previous prospective study, Pettitt et al did not find worsening of existing diabetic retinopathy, despite significant improvements in glycemia. The demographics of that population were almost identical in racial/ethnic balance, age (~55 yrs), duration of diabetes (8-11 yrs), duration of follow-up (~22 months), and baseline hyperglycemia (HbA1C~9.7%. The critical difference between the studies is the degree of improvement in glycemic control. The reduction in mean HbA1C in the earlier case-management study was less than 2% from baseline (11,12) in contrast to 4% that occurred here. In that study, the mean HbA1C achieved by intervention was 7.8%(11). Thus, a <2% decrement in HbA1C, and/or to levels that remain above 7.8% in poorly controlled patients (11), appears safer than a 4% drop (to a mean of 6.7% seen in this study in the same population.

Acceleration of diabetes complications with tightening glucose control may not be confined to microvascular disease. Findings in the ACCORD study raise the possibility that a similar phenomenon may occur in cardiovascular disease (CVD) in Type 2 diabetes (6-8). The appearance of increased mortality in the tight glycemic control arm in type 2 diabetic patients is consistent with the microvascular findings in this study, and suggests that a worsening outcome in response to vigorously managed glycemia may be a factor in those observations as well (6). Post-hoc analysis of the Veterans Administration Cardiovascular trial also supports the idea that tight glucose control in patients with long-duration diabetes and highest risk for CVD might have a deleterious impact (8,16,17). CVD response to tight glycemia may have a different course to retinopathy. The worsening observed in type 1 diabetes in the DCCT occurred early in the trial as it did in the current study and was not seen in ACCORD after four years of follow-up (18). Early, perhaps transient worsening of retinopathy, if it occurred in ACCORD may have been missed (18).

Limitations of this study include the fact that it is retrospective, and thus not randomized. Also, worsening retinopathy could be attributed to the poor initial glycemic control in the intensive group. This is unlikely, considering that this group started out with less retinopathy despite worse glycemia. Furthermore, when a subset of the control group with poor glycemic control was evaluated, retinopathy worsening was not observed. It is therefore likely that the combination of poor initial control and subsequent rapid and substantial decrement in HbA1C levels together account for the deterioration, rather than either phenomenon alone. An additional study limitation is the use of a single field rather than seven fields for evaluation of the retina. However, this technique has been shown to be effective for diabetic retinopathy screening and follow-up studies (12,19). Baseline and follow-up retinal fields are identical, so it is likely that our findings reflect clinically meaningful change in retinopathy. Another limitation is the relatively small size of this study. Larger studies are important for generalizability, but may be difficult to implement in

the foreseeable future given the potential CVD risks observed when dramatic changes in glycemic control occurs in patients with established diabetes (6).

In summary, we have demonstrated that despite similar average HbA1C concentrations over a two-year period, substantial improvement of poor glycemic control is associated with significant worsening of retinopathy in predominantly minority Type 2 diabetic patients. Prior diabetes duration appears to be less important for deterioration in retinopathy than decrement in HbA1C. In this study, no sight was lost due to progression of retinopathy; this may not be the case if patients have sight-threatening disease when intensive therapy is introduced. These results should not discourage intensive glycemic control in patients with type 2 diabetes. Carefully individualized management that takes into account risk factors for worsening should be used (8). In a setting where poorly controlled type 2 diabetes is treated with effective management strategies, careful evaluation of each patient should take place prior to intensification of glycemic control.

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Abbreviations used in the manuscript

HbA1C	Hemoglobin A1c
DCCT	Diabetes Control and Complications Trial
CVD	Cardiovascular Disease
UKPDS	United Kingdom Prospective Diabetes Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes

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TABLE 1

BASELINE CHARACTERISTICS OF PATIENTS

	Intensive (n = 34)	Control (n = 34)	p Value
Age (Years)	52 ± 2.2	52.3 ± 1.95	0.99
Sex (F/M)	15/19	17/17	0.627
% Ethnicity (Latino/White/Other)	19/11/4	26/3/5	0.06
Diabetes Duration (Years)	8.4 ± 1.12	13.1 ± 1.52	0.017
Treatment (Orals, Insulin) *	20/23	27/18	0.292
Hypertension (n)	25	22	0.431
Duration of Follow-Up (Months)	24.7 ± 2.3	26.7 ± 2.45	0.55
Creatinine (mg/dl)	1 ± 0.1	0.9 ± 0.06	0.25
Total Cholesterol (mg/dl)	184 ± 10	176 ± 5.3	0.47
LDL Cholesterol (mg/dl)	114 ± 5.7	107 ± 4.7	0.30
HDL Cholesterol (mg/dl)	36 ± 1.9	39 ± 1.5	0.18
Triglycerides (mg/dl)	186 ± 29.1	208 ± 26.4	0.58
Systolic Blood Pressure (mm Hg) **	130 ± 4.5	120 ± 4.3	0.13

Mean ± SEM

*, Treatment of diabetes during the study. Patients were on oral agents, insulin or both so that the total number on either orals or insulin adds up to more than 100%.

**, Systolic Blood Pressure measurements were available from n=23 intensive and n=24 control subjects.

TABLE 2

EFFECT OF HbA1c LOWERING ON RETINOPATHY GRADE

	Intensive	Control	p value	
	(n=34)	(n=34)	within group	between group
Duration of Follow-up (mos)	24.7 ± 2.3	26.7 ± 2.45	<>	0.55
A1C (%) [mmol/mol]				
Baseline	10.7±0.35 [93]	7.9±0.27 [63]	<>	<0.001
Maximum decline	4.0±0.41 [20]	0.2 ± 0.11	<>	<0.001
Time to max decline (mos)	13.4 ± 2.22	9.8 ± 1.77	<>	0.21
Average A1C overall *	8.5±0.21 [69]	8.1±0.28 [65]	<>	0.3
Retinal Grading (units **)				
Baseline Retinopathy ***	16 of 34	12 of 34	<>	0.14
Baseline images	3.1 ± 0.32	3.9 ± 0.43	<>	0.12
Final images	3.8 ± 0.35	3.9 ± 0.42	I = 0.015 C = 0.87	0.79
Change in Grade	0.7 ± 0.25	0.03 ± 0.14	<>	0.02

Mean ± SEM

Abbreviations: I = Intensive group; C = Control group, mos = months

* = Average of HbA1C over duration of study (includes start HbA1C, final HbA1C around time of obtaining images and lowest intervening HbA1C).

** = Assigned units using a modified Scottish Diabetic Retinopathy Grading Scale (see methods)

*** = Number of subjects with pre-existing retinopathy at baseline.