Ocular changes in insulin-dependent diabetic patients: Risk factors

Iman M. Marzouk,[1] Mohamed A. Ragab, Mohamed Fathy El Sahn, Salah A. Marzouk,[2] and Ossama A. Ismail

From the departments of Pediatrics,[1] Ophthalmology, and Clinical Pathology,[2] Faculty of Medicine, University of Alexandria, Egypt.

Abstract:

This work aimed at finding out the frequency of different ocular changes in insulin dependent diabetic patients and the relation – if any- between the present abnormalities and some of the suggested risk factors. The study was carried out on 40 insulin dependent diabetic patients ranging in age between 6.5 and 2 4 years and 10- age and sex- matched non-diabetic persons taken as control. Fifty percent of the studied eyes of diabetic patients had at least one abnormality. The presence of non-leaking microaneurysms was the most frequently observed one (52.5%), followed by conjunctival microvascular abnormalities (25%), then premature detachment of vitreous (22.5%) and leaking microaneurysms (22.5%). Ocular changes were significantly more frequent among older diabetic patients (≥15 years of age), diabetics with longer duration of the disease (>4 years), and those with uncontrolled diabetic state (HbA1c ≥ 8.75%). Diabetic children less than 15 years of age who developed ocular abnormalities had significantly higher serum levels of triglyceride (TG) and very low density lipoproteins (VLDL) than those with no ocular changes. Diabetic patients aged more than 15 years, with ocular abnormalities, had significantly higher glycosylated hemoglobin (HbA_{1c}) concentrations and longer duration of diabetes mellitus. It was concluded that the long-term glycemic control and the duration of diabetes mellitus were the major risk factors for the development of ocular changes among diabetics.

Introduction:

Abnormalities with variable clinical significance are known to occur in nearly every anatomic subdivision of the eye in diabetic patients. Much controversy exists regarding the pathogenesis of angiopathy, the most common disabling complication of insulin dependent diabetes mellitus (IDDM).[1] Long duration of diabetes including the prepubertal years and poor metabolic control during puberty are well recognized risk factors for the development and progression of retinopathy in young diabetic patients.[2] The role of dyslipoproteinemia as a co-factor with hyperglycemia, glycosylated proteins, and growth hormone in the pathogenesis of diabetic retinopathy is unknown.[2,3,4] However, lipid abnormalities can contribute to endothelial damage and thereby exacerbate small vessel disease.[3] This work aimed at finding out the frequency of different ocular changes in insulin dependent diabetic patients and the relation –if any- between the present abnormalities and some of the suggested risk factors.

Subjects and methods:

The study was carried out on 40 insulin- dependent diabetic patients ranging in age between 6.5 and 24 years. They were classifieds according to the average of age (±15 years) and were age and sex matched with 10 non-diabetic persons who served as control.

All the included individuals were subjected to the following:

1. History taking and general clinical examination.
2. Ophthalmologic examination including:
   - Best corrected visual acuity and cycloplegic refraction.
   - Measurement of intraocular pressures using Schioetz tonometer after surface anesthesia.
   - Slit lamp biomicroscopy to examine the anterior ocular structures to a depth of the anterior vitreous.
   - Funduscopy and slit lamp biomicroscopy with Goldman three-mirror contact lens or the 90-diopter fundus lens.
   - Fluorescein angiography was done when possible using a 50- degree fields fundus camera. Fundus photography was taken for some of the suitable cases by using Kodak Ektachrome-X colored films.
3. Laboratory investigations: fasting blood samples were taken for measuring of:
   - Blood glycosylated hemoglobin (HbA_{1c}) concentrations. [5] Uncontrolled diabetic state were considered at 95%

confidence limit ($HbA_{1c} \geq X+2SD$ of the non diabetic values).

- Basal serum growth hormone (GH) levels by radioimmunoassay (RIA).[6]
- Serum levels of cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). [7]

Results:

- There was no significant difference in the visual acuity among the studied eyes of diabetic and control subjects (table I).
- Ocular changes were detected in 55% of the eyes of diabetic patients. The presence of non-leaking microaneurysms, diagnosed by fluorescein angiography, was the most frequently observed ocular abnormality. (52.5%) (table II and fig. 1).
- Ocular changes were significantly more frequent among diabetics with poor diabetic control ($HbA_{1c} \geq 8.75\%$) and those with longer duration of the disease (>4years) (table III).
- Diabetics, whatever their age group, had significantly higher levels of $HbA_{1c,}$ GH, cholesterol, LDL, VLDL, and lower levels of HDL than non diabetic group (table IV).
- When compared with diabetics with controlled diabetic state and control group, diabetic patients with uncontrolled diabetic state had the highest GH levels. On the other hand, there was no effect of the state of diabetic control on the other metabolic parameters (table V).
- Diabetics who developed ocular abnormalities had basal growth hormone levels more or less equal to those who did not show any of these abnormalities (table VI).

Table I: Refractive state of the studied eyes.

	Diabetics		Control		Z test values
	Nº	%	Nº	%	
Emmetrope	53	66.3	12	60.0	0.35
Myope	17	21.2	4	20.0	0.12
Hypermetrope	6	7.5	3	15.0	1.09
Astigmatism	4	5.0	1	5.0	0.001
Total	80	100	20	100	

Table II: Frequency of ocular abnormalities observed in the studied diabetic eyes.

	Eyes of diabetics ≤ 15 years of age		Eyes of diabetics > 15 years of age		Total	
	Nº(40)	%(100)	Nº(40)	%(100)	Nº(80)	%(100)
Conjunctival microvascular abnormalities	2	5	18	25	20	25
Slow pupillary dilatation	0	0	10	25	10	12.5
Premature detachment of the vitreous	2	5	16	40	18	22.5
Microaneurysms:						
By direct ophthalmoscopy:	0	0	4	10	4	5
By fluorescein angiography :						
Non-leaking	18	45	24	60	42	52.5
Leaking	3	7.5	15	37.5	18	22.5
Venous dilatation	2	5	11	27.5	13	16.25
Focal maculopathy	0	0	10	25	10	12.5
Total eyes with ocular changes	18	45	26	65	44	55

Table III: Distribution of ocular abnormalities among diabetics

	Diabetics with Ocular abnormalities Nº(22)	%(100)	Z test values
Age ≤ 15 years	9	40.9	
> 15 years	13	59.1	1.12
Duration of diabetes			
≤ 4 years	6	27.25	4.12*
> 4 years	16	72.75	
State of diabetic control:			
HbA 1c < 8.75%	2	9.09	6.12**
≥ 8.75%	20	90.91	

** Significant at 1% level of significance, ** Significant at 0.1% level of significance*

Table IV: Comparison between laboratory findings in diabetic and control groups

	Diab.≤15 years (n=20) X±SD	Control≤15 years (n=5) X±SD	t test values	Diab.>15 years (n=20) X±SD	Control>15 years (n=5) X±SD	t test values
HbA_{1c} (%)	10.4±1.8	6.8 ±7.5	3.26*	11.2 ±1.8	7.9 ±0.2	4.66**
GH(uIU/ml)	4.9± 4.6	1.4±0.6	3.66*	1.9± 1.9	0.8± 0.7	3.68**
Cholest. (mg/dl)	246.1± 44.2	181.0± 15.2	8.99**	267.5±48.2	180.0 ±12.7	8.65**
TG (mg/dl)	110.3± 14.2	78.0 ±30.7	7.89**	115.5± 23.1	93.0± 23.3	6.32*
HDL(mg/dl)	62.1± 23.5	71.0± 4.2	3.52*	49.4 ±9.9	78.4± 12.9	9.65**
LDL(mg/dl)	161.9± 62.8	94.4± 21.8	5.96*	195.0± 62.3	83.0± 17.3	12.4**
VLDL(mg/dl)	22.1± 2.8	17.1± 5.4	3.12*	21.3± 4.6	17.1± 5.4	3.14*

* Significant at 5% level of significance, ** Significant at 1% level of significance

Table V: Comparison between laboratory findings in respect to the state of diabetic control.

	Diab. with controled diabetic state (HbA_{1c}<8.75%) (n=7) X±SD	Diab. with uncontroled diabetic state (HbA_{1c}≥8.75%) (n=33) X±SD	Control group (n=10) X±SD	F test values & sites of significance
GH(uIU/ml)	2.5± 3.6	3.6± 3.9	1.1± 0.7	3.2* (1,2)(1,3)(2,3)
Cholest.(mg/dl)	237.1± 48.8	260.9±46.2	180.5 ±13.2	2.o1
TG (mg/dl)	111.7 ±18.6	118.6± 21.9	85.5± 26.9	2.33*(1,3)(2,3)
HDL(mg/dl)	63.1± 24.8	54.2± 21.8	74.7± 9.9	4.01*(1,3)(2,3)
LDL(mg/dl)	150.3± 70.6	184.5± 62.0	88.7± 19.5	5.24*(1,3)(2,3)
VLDL(mg/dl)	23.7± 4.3	22.3± 3.7	17.1 5.4	2.31*(1,3)

** Significant at 5% level.*

Table VI: Comparison between laboratory findings in respect to the occurrence of ocular abnormalities

	Diab.≤15 y with ocular ab. (n=9) X±SD	Control≤15 y with ocular ab. (n=11) X±SD	t test values	Diab.>15 y with no ocular ab (n=13) X±SD	Control>15y with no ocular ab(n=7) X±SD	t test values
GH(uIU/ml)	1.9 2.4	1.8 1.2	0.48	4.9 4.3	5.0 5.8	0.89
Chol. (mg/dl)	250.0 43.5	241.3 47.2	1.12	270.3 49.1	259.0 49.9	0.99
TG (mg/dl)	116.8 10.8	102.2 14.6	2.4*	113.3 25.0	122.0 17.0	0.89
HDL(mg/dl)	57.7 24.9	67.4 22.0	0.98	47.5 17.8	55.0 25.5	0.78
LDL(mg/dl)	168.9 62.8	153.4 65.5	0.78	200.1 59.6	179.6 74.9	0.74
VLDL(mg/dl)	23.4 2.06	20.4 2.9	2.6*	22.7 4.7 4.9	24.4 3.4	1.00

** Significant at 5% level.*

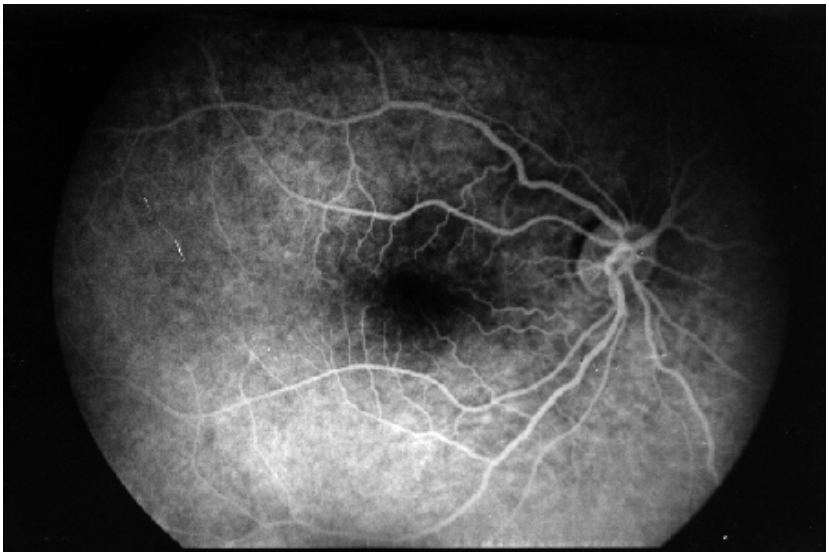

Fig 1: (a) Focal maculopathy

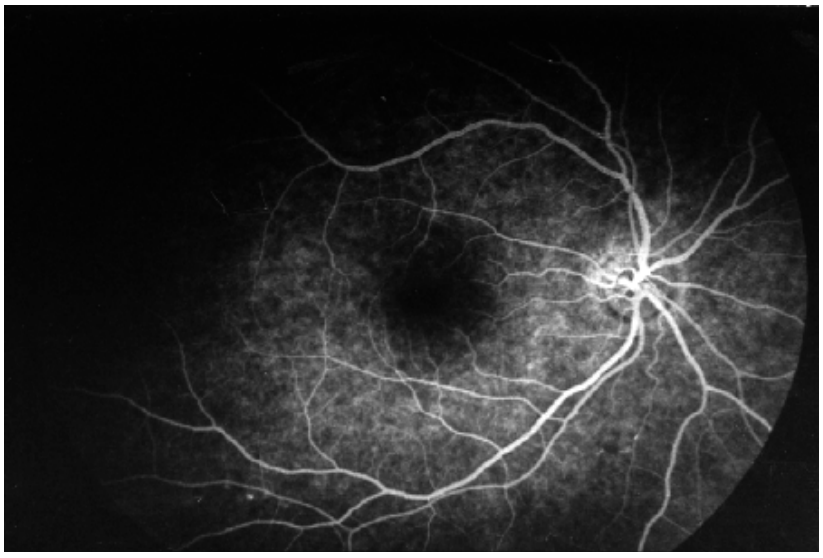

Fig 1: (b)Leaking microaneurysms.

Discussion:

The observed greater sensitivity of fundus fluorescein angiography in the diagnosis of mild non-proliferative diabetic retinopathy as opposed to photography can be explained by two theoretical arguments. First, angiograms present small lesions in greater contrast than do photographs. A microaneurysm appears on a positive print as a white dot, easily distinguished from the black background, while in photograph it is red, often hard to separate from the orange background. Second, a microaneurysm may appear smaller by photography than by angiography. Its red color is produced by erythrocytes in the center of the lumen. If a shell of transparent plasma surrounds these, the lumen may actually appear larger by angiography, since the fluorescein occupies the entire plasma space and may in addition stain the endothelial wall of the aneurysm.[8] In accordance to our results, it was reported that when retinopathy does occur in childhood or adolescence, it is usually minimal background retinopathy manifest as microaneurysms alone.[9] Moreover, Ferman [10

)added that after the onset of microaneurysms, several years may pass before any other diabetic retinopathic lesions develop.

The frequency of maculopathy among the studied diabetics in our study, was in agreement with Wisconsin Epidemiologic Study of diabetic retinopathy (WESDR).[11] Also, the observed difficult pupillary dilatation was in accordance to what reported that the pupil in patients with diabetic neuropathy is difficult to dilate by the use of atropinic agents and the addition of a directly acting sympathomimetic to which the pupil is supersensitive, may improve the mydriasis. The normal range of intraocular pressure in the studied eyes of diabetics could be explained by the unaffected dynamics of aqueous humour to any clinically significant extent in the early or middle stage of diabetic retinopathy. [12]

As expected, ocular abnormalities were more frequent with increased age and duration of diabetes mellitus. Frank et al.[13] did not diagnose retinopathy in their diabetic patients aged from 5 to 9 years. It was diagnosed in only 16% of diabetics aged from 10 to 24 years and 84% of those were above 15 years old. Also, Pinto et al.[14] stated that the prevalence of retinopathy in a population of 1302 insulin dependent diabetics diagnosed before 30 years of age increases with the duration of the disease. The relationship between the occurrence of abnormalities and the state of diabetic control, that was observed in this work, was confirmed by Holl et al. [15] who noticed a delay of almost 3 years in the onset of retinopathy in those with an HbA_{1c}< 7.5%. Also, it was reported that higher HbA_{1c} levels significantly increase the risk of clinically significant macular edema in persons with type I diabetes.

In accordance to our results, Cutfield[16] reported that poor glycemic control leads to higher growth hormone levels. Alzaid et al.[4] suggested that GH contributes to the diabetic retinopathy, which was not proved in our work. However, the presence of higher TG levels in young diabetics who developed ocular changes was in agreement with Lioyd et al. [17] who suggested that serum TG was associated with the progression of retinopathy. Also, it was reported that patients who had elevated serum VLDL were more likely to develop retinal hard exudate. Dune et al.[18] found that insulin therapy lowered VLDL levels which were elevated in our young diabetics who developed ocular changes.

It was concluded, from the present study, that best metabolic control of diabetes mellitus should be sought to get the least ocular abnormalities. Measurement of blood HbA_{1c} should be done routinely for evaluation of the glycemic control and serum lipids should be determined for better dietary control of diabetic patients. Fluorescein angiography is to be done even for diabetic children to be taken as base line determinant of the state of retina in addition to the frequent fundus examination. So, close co-operation between pediatricians, internists and ophthalmologists is necessary to keep vascular complications to a minimum and to detect them early.

References:

1. Kokkonen J, Latikainen L, Dickohoff K. Ocular complications in young adults with insulin-dependent diabetes mellitus since childhood. Acta Paediatrica 1994; 83: 273-8.
2. Kullberg CE, Finnstrom K, Arnqvist HJ. Severity of background retinopathy in type I diabetes increases with the level of long term glycosylated hemoglobin. Acta Ophthalmologica 1994, 72: 181-8.
3. Sinav S, Onelge MA, Onelge S, Sinav B. Plasma lipids and lipoproteins in retinopathy of type I (insulin- dependent) diabetic patients. Annals of Ophthalmol 1993; 25: 64-6.
4. Alzaid AA, Dinneen SF, Melton LJ, Rizza RA. The role of growth hormone in the development of diabetic retinopathy. Diabetes care 1994; 17: 531-4.
5. Klein R. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. JAMA 1988; 260: 2864-71.
6. Celinker A, Chen A, West R. Variability in the quantitation of circulating growth hormone using Commercial immunoassays. J Clin Endocrinol Metab 1989; 68: 469-76.
7. Evan A, Myers GL, Teitz M. Fundamentals of clinical chemistry. 4th ed 1996; 397-405.
8. Hellstedt T, Immonen I. Disappearance and formation rates of microaneurysms in early diabetic retinopathy. Br J Ophthalmol 1996; 80: 135-9.
9. Kernell A, Dedorsson I, Johansson B, Wichstrom CP, Ludvigsson J, Tuvemo T. Prevalence of diabetic retinopathy in children and adolescents with IDDM: a population based multi-center study. Diabetologia 1997; 40: 307-10.
10. Ferman SS. The natural history of the first clinically visible features of diabetic retinopathy. Transactions of the American Ophthamological Society 1994; 91: 1464-74.
11. Klein R, Klein BEK, Moss SE, Davis MD, De Mets DL. The Wisconsin Epidemiologic Study of Retinopathy. VI. Diabetic macular edema. Ophthalmology 1984; 91: 1464-74.

12. Larsson LI, Pach JM, Brubaker RF. Aqueous dynamics in patients with diabetes mellitus. Am J Ophthalmol 1995; 120: 362-7.
13. Frank RN, Hoffman WH, Podger MJ. Retinopathy in juvenile onset type I diabetes in insulin- dependent juvenile – onset diabetes. Diabetes 1982; 31: 874-82.
14. Pinto FL, Moita J, Genro V, Vinagre M, Laires R, Rosa MJ. Cardoso C, Carrieras F. Diabetic retinopathy in a population of 1302 insulin dependent diabetics (IDDM) diagnosed before 30 years of age. International Ophthlmology 1992; 16: 429-37.
15. Holl RW, Lang GE, Grabert M, Heitz E, Lang GK, Debatin KM. Diabetic retinopathy in pediatric patients with type I diabetes: effect of diabetes duration, prepupertal and pupertal onset of diabetes, and metabolic control. J Pediatr 1998; 132: 790-4.
16. Cutfield W. Screening for diabetic retinopathy in chidhood. J Pediatr 1998; 132: 760-2.
17. Lioyd CE, Klein R, Maser RE, Kuller LH, Becker DJ, Orchard TJ. The progression of retinopathy over 2 years: The Pittsburg Epidemiology of Diabetes Complications (EDC) Study. J Diabetes and its Comp 1995; 9: 140-8.
18. Dune FL. Plasma lipids and lipoprotein disorders in IDDM. Diabetes 1992; 41: 102-