Eye Complications in Children and Adolescent with Type 1 Diabetes Mellitus

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ABSTRACT:

BACKGROUND:

Diabetes mellitus is characterized by hyperglycemia and glycosuria and is an end point of a few disease processes. The most common type occurring in childhood is type 1 DM, which is accompanied by chronic and dangerous micro vascular changes affecting most body systems, especially the eye, leading to cataract and diabetic retinopathy. Diabetic retinopathy without appropriate management is emerging as one of the leading causes of blindness. Therefore, it is necessary to identify relevant risk factors, improve the early diagnosis and management of diabetic retinopathy to reduce the risk of blindness.

OBJECTIVE:

To estimate the presence of eye complications (cataract and retinopathy) among children and adolescent with type1 diabetes mellitus and to study the effect of various factors on their occurrence.

PATIENTS AND METHODS:

This study was carried out over nine months period(from first of May till the end of January) at Children Welfare Teaching hospital/Medical City .It included 150 children who had type1diabetes mellitus for at least 4 years in children with pre pubertal onset of diabetes and two years in children with pubertal onset .History was taken, physical examination and investigations were done, then ophthalmological examination looking for eye complications (cataract or retinopathy) performed by ophthalmologist. Statistical analysis done using T test, Chi square, P value <0.05 regarded as statistically significant

RESULTS:

This study included 150 patients with type 1 diabetes mellitus, their age ranges from 4.5 - 19 years, with duration ranges from 2-18 years. Female to male ratio was 1.8:1.Out of 150 diabetic patients, 24/150 (16%) had eye complications, 9 (6%) of them had retinopathy while other 15 (10%) had cataract .The age of all patients who had eye complication was >10 years which is highly significant (P value: 0.009) and the incidence of eye complications increases with increasing duration of diabetes (p value 0.04). Twenty two (14.7%) female and two (1.3 %) male had eye complications, which is highly significant (P value: 0.002). HbA1c $\geq$10 in 17/24 (70.8%) patients with eye complications. there were significant association between the presence of eye complications and macroalbuminuria (p value: 0.02), and limited joint mobility (p value: 0.001) .out of 24 patients with eye complications, 16 (66.6%) patients had short stature and 7(4.7%) patients had celiac disease.

CONCLUSION and recommendations:

The incidence of eye complications (cataract and diabetic retinopathy) increases with increasing age and duration of diabetes and it is more common in female and it is associated with the presence of other chronic complications (LJM, nephropathy and short stature).So screening all patients with type 1 DM according to the guidelines is required for early detection and treatment of eye complications using new methods like fundal photography.

KEY WORDS: type 1 DM, eye complications, diabetic retinopathy, cataract, .

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INTRODUCTION:

Diabetes mellitus (DM) is characterized by hyperglycemia and glycosuria and is an end point of a few disease processes. The increasingly prolonged survival of the diabetic child is associated with increasing prevalence of complications [(1)].

The risk of diabetic retinopathy after 15 year duration of DM is 98 % for individuals with type 1 DM and 78%for those with type 2DM, Lens opacities are present in at least 5% of those younger than 19 year of age[2,3]. Cataract is the leading cause of blindness in the world[4].Diabetes mellitus is one of risk factor associated with acquired cataract in developed nation[5].Modern microsurgical technique allows intervention for cataract before it has resulted in blindness; normal vision typically is restored with intraocular lens implantation[6]. Retinopathy is a major cause of morbidity in patients with type 1 and 2 diabetes. The incidence of blindness, for example, is 25 times higher in patients with diabetes than in the general population. Furthermore, diabetic retinopathy (DR) is the most common cause of blindness in middle-aged subjects, accounting for at least 12000 new cases in the United States each year. Visual loss from diabetic retinopathy may be secondary to macular edema, hemorrhage from new vessels, retinal detachment, or neovascular glaucoma [7].

The prevalence of DR has significantly decreased as intensive insulin therapy for the management of type 1 diabetes has become more widespread. The severity of DR has decreased as well, with only 10 percent of retinopathy patients found to have moderate or severe nonproliferative retinopathy (NPDR) in the Wisconsin study [8].

The pathogenesis of DR is multifactorial but is primarily caused by the metabolic effects of chronic hyperglycemia, which result in vascular changes and subsequent retinal injury and ischemia [9].Two proposed contributed factors are advanced glycosylation end products (AGEs) and sorbitol [10]. Genetic predisposition may be another important factor. Genetic influences affect the severity of retinopathy as sever retinopathy was three times more frequent among the relatives of retinopathy-positive patients than the retinopathy-negative patients [11]. More advanced retinal disease, including proliferative vascular changes and neovascularization in the setting of retinal ischemia, may be mediated by other mechanisms such as the action of vasoactive substances released during the inflammatory process[10].There was a continuous relation between the degree of glycemic control and the incidence of retinopathy (the only complication for which such data were reported): the rate of progression increased from one per 100 patient-years at a mean A1c value of 5.5 percent up to 9.5 per 100 patient-years at a mean A1c value of 10.5 percent ;progressive retinopathy was uncommon at A1c value below 7 percent[11]. In addition to its efficacy in primary prevention, intensive insulin therapy also slows the rate of progression of mild to moderate retinopathy [12]. Diabetic retinopathy is divided into two major forms: non proliferative and proliferative, named for the absence or presence of abnormal new blood vessels emanating from the retina. Each patient with diabetic retinopathy has a unique combination of findings, symptoms, and rate of progression, which necessarily requires an individualized approach to treatment in the effort to preserve vision [7]. Non proliferative retinopathy (NPDR) consists of a variable display of nerve-fiber layer infarcts (cotton-wool spots), intra retinal hemorrhages, and hard exudates, and micro vascular abnormalities (including micro aneurysms, occluded vessels, and dilated or tortuous vessels) primarily in the macula and posterior retina.Visual loss in non proliferative retinopathy is primarily through the development of macular edema (ME)(17). Proliferative diabetic retinopathy (PDR) is marked by the presence of neo vascularization arising from the disc and/or retinal vessels [7] . The consequences of this neovascularization, including pre retinal and vitreous hemorrhage, subsequent fibrosis, and traction retinal detachment. Visual loss in PDR may occur acutely if bleeding from the abnormal vessels into the vitreous blocks the light path to the retina; however, the blood is often reabsorbed and vision clears spontaneously. More permanent loss of vision may occur through retinal detachment, ischemia of the macula, or combinations of these factors. The severity of proliferative retinopathy can be classified as early, high risk, and severe. Untreated high risk proliferative retinopathy results in a 60 percent risk of severe vision loss at five years [7]. Macular edema can be present with any degree of proliferative retinopathy and should be addressed as part of the overall treatment strategy [10].

Clinical manifestation: The vast majority of patients who develop diabetic retinopathy have no symptoms until the very late stages (by which time it may be too late for effective treatment). Because the rate of progression may be rapid, and therapy can be beneficial for both symptom amelioration and reduction in the rate of disease progression, it is important to screen patients with diabetes regularly for the development of retinal disease [13].

It is suggested that diabetic patients have an initial detailed and comprehensive examination

by an ophthalmologist s within 2-5 years after the onset of type 1 DM (after 5 years in pre pubertal children, after 2 years in pubertal children but not before age 10 years). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both type 1 and type 2 DM patients should be repeated annually by an ophthalmologist [(1)]. Other complications in diabetic children include dwarfism and the syndrome of Limited joint mobility (LJM) , which is one of the earliest and most common clinical complications in type 1diabetes, and it is frequently associated with the early development of diabetic micro vascular complications , such as retinopathy and nephropathy , which may appear before 18 year of age [(1)].The association between the development of DR and nephropathy, independent of the degree of hyperglycemia and the duration of diabetes, suggests that common pathogenetic factors may underlie the development of both complications. The presence of albuminuria was a significant predictor for retinopathy (as detected via stereoscopic retinal fundus photography) [(14)].In this study we intend to estimate the presence of eye complications (cataract and retinopathy) among children and adolescent with type1 diabetes mellitus and to study the effect of various factors on their occurrence.

PATIENTS AND METHODS:

This study was carried out over nine month's period (from the first of May 2012 till the end of January 2013). It included 150 children who had type1diabetes mellitus for at least 4 years in children with pre pubertal onset of diabetes and two years in children with pubertal onset who were admitted to Children Welfare Teaching Hospital / Medical City for the management of diabetes and those consulting the diabetic clinic for monitoring of their diabetes. The following data were collected: age (date of birth), date of admission or consultation, date of onset of diabetes and so duration of diabetes was calculated, sex, glycemic control (last year hemoglobin A1c), family history of type 1 diabetes mellitus, and eye problems, and history of other diseases or complications related to diabetes mellitus (celiac disease, limited joint mobility, and nephropathy). Any patient with positive family history for eye problems was excluded. Physical examination was carried out for each patient, which includes: Blood pressure, weight, height, which applied to Tanner growth chart and any patient with height below 3rd centile regarding as short stature, limited joint mobility, and systemic examination. Ophthalmological examination included (visual acuity, anterior segment examination by slit lamp and fundoscopic examination of the posterior segment through dilated pupils) was done in the ophthalmology clinic of the Medical City. The pubertal age of male start at age of (9.5) years, and for female at age of (8) years. The adolescent period extend from the age of (10-20) years and it divided into early, middle and late adolescence [(1)]. Blood pressure (B.P) was measured by using sphygmomanometer with appropriate cuff size for age and using CDC (central diseases control) age specific percentile of blood pressure in boys and girls, and considered hypertensive when the reading above the 95th percentile for age.

Limited joint mobility (LJM): was assessed by using prayer maneuver; patients were asked to approximate the palmer surfaces of the fingers in a praying position with the fingers fanned and the wrists flexed. If the patient failed to approximate the palmer surfaces completely, the examiner attempted to extend the fingers passively. Equivocal ,or unilateral , findings or simply a sense of resistance without limitation was classified as no LJM .The failure of any joint to make contact was classified as LJM [(15)]. Regarding lab investigations; Blood samples were collected as follows: Two ml were taken into vacuum collection tube containing EDTA and thoroughly mixed for estimation of HbA1c which was estimated by using fast ion-exchange Resin separation Method, using record package, from Human Gesellschaft fur Biochemical and DiagnosticambH .Germany [(16)]. Another blood sample was taken to screen for Celiac disease. This work was done in the biochemistry department of teaching laboratories of Medical City. Regarding glycemic control, we took the HbA1c as indicator for glycemic control in which we have either: Good control with (HbA1c= 6-7.9), Fair controls with (HbA1c= 8- 9.9).Poor control with (HbA1c $\geq$ 10)[(1)]. Urine sample was collected from each patient and analyzed by using the method of (Turbid metric test) for the quantitative determination of macroalbumine in Human urine in which the urine sample centrifuged, supernatant was taken to which few drops of sulfo - salicylic acid was added , finally the turbidity examined by naked eye (ranged from trace - 4plus).Statistical analysis: Spss program was used for statistical calculation, chi-

square (X^2) test was carried out to determine the relative importance of various variables, T-test was carried out to compare between two samples proportion. P- value less than (0.05) was considered as statistically significant(s),value less than (0.01) was considered to be highly significant (HS),and less than(0.001) as extremely significant(ES) .

RESULTS:

This study include 150 patients with type 1 diabetes mellitus attending the diabetic clinic of children welfare teaching hospital/ medical city. Their age ranges from 4.5 - 19 years, with a mean of 14.6 years and median of 15 years, the duration of the disease ranges from 2-18 years, with a mean of 6.8 years, and median of 7 years. Out of 150 diabetic patients, 24/150 (16%) had eye problem, 9 of them had retinopathy while other 15 had cataract (table No.1)

Table No 1: The incidence of eye problem in 150 patients with type I DM.

Eye complications	No.	%
Proliferative retinopathy	7	4.7
Non proliferative retinopathy	2	1.3
Cataract	15	10
Total	24	16

All diabetic patients who had eye complications were >10 years 0f age, which is highly significant (p value = 0.009) (Table No.2).

Table No 2: Correlation between age and eye complications in patients with type1DM.

Age(years)	No Eye complications(%)	Eye complications(%)	total (%)	P value
< 5	1(0.7)	0	1(0.7)	
>5-10	16(10.7)	0	16(10.7)	
>10-15	69(46)	8(5.3)	77(51.3)	0.009
>15	40(26.7)	16(10.7)	56(37.3)	
total	126(84)	24(16)	150(100)	

out of 150 diabetic patients included in the study, 97 were female, with female to male ratio of 1.8:1. The eye complications were more in female (14.7%) than male (1.3 %) (P value 0.002) (Table No.3).

Table No 3: Correlation between sex and eye complications in patients with type1DM.

sex	No Eye complications(%)	eye complications(%)	Total	P value
Male	51(34)	2(1.3)	53(53.3)	
Female	75(50)	22(14.7)	97(64.7)	0.002
Total	126(84)	24(16)	150(100)	

The incidence of eye complications increases with increasing duration of diabetes (p value 0.04). There were 4 patients had eye complications with duration of diabetes less than 5 years, all of them had pubertal onset of diabetes (Table 4).

Table No 4: Correlation between duration of type 1DM and eye complications.

Duration	No Eye complications(%)	Eye complications(%)	Total (%)	P value
< 5	38(25.3)	4(2.7)	42(28)	
5-10	77(51.3)	14(9.3)	91(60.7)	
>10	11(7.3)	6(4)	17(11.3)	0.04
total	126(84)	24(16)	150(100)	

Out of 24 patients with eye complications, 17 (70.8%) patients had HbA1c ≥10 (table 5).

Table No 5: Correlation between HbA1c level and eye complications in patients with type 1 DM.

HbA1c level	No Eye complications(%)	Eye complications(%)	Total (%)	P value
6-7.9	1(0.7)	0	1(0.7)	0.3
8-9.9	55(36.7)	7(4.7)	62(41.3)	
≥10	70(46.7)	17(11.3)	87(58)	
total	126(84)	126(16)	150(100)	

Out of 24 patients with eye complications, 8 (33.3%) patients had macroalbuminuria with significant association between presence of macroalbuminuria and eye complications (p value 0.02) (Table 6).

There was significant association between presence of limited joint mobility and eye complications in patients with type1DM (P value: 0.001) (Table 6).

Out of 24 patients with eye complications, 16/24(66.7%) had short stature (height below 3rd centile) and 8/24 (33.3 %) had normal height (Table 6).

Table No 6 : the association between eye complications and other chronic complications of type 1 diabetes mellitus.

Chronic complications of T1DM	Eye complications(%)	No eye complications (%)	Total(%)	P value
macroalbuminuria negative	16(10.7)	110(73.3)	126(84)	0.02
macroalbuminuria positive	8(5.3)	16(10.7)	24(16)	
Limited joint mobility negative	6(4)	79(52.7)	85(56.7)	0.001
Limited joint mobility positive	18(12)	47(31.3)	65(43.3)	
Height < 3rd centile	16(10.7)	62(41.3)	78(52)	0.2
Height 3rd - 97th centile	8(5.3)	63(42)	71(47.3)	
Height >97th centile	0	1(0.7)	1(0.7)	

There was no significant association between the presence of celiac disease and eye complications in patients with type1DM (P value= 0.4). (Table. 7).

Table No 7: The association between celiac disease and eye complications in patients with type 1 DM.

Celiac disease	No eye complications (%)	Eye complications (%)	Total (%)	P value
negative	100(66.7)	17(11.3)	117(78)	0.4
Positive	26(17.3)	7(4.7)	33(22)	
Total	126(84)	24(16)	150(100)	

DISCUSSION:

Morbidity from diabetes is a consequence of both macro vascular disease (atherosclerosis) and micro vascular disease (retinopathy, nephropathy, and neuropathy). Epidemiologic studies first showed an association between poor glycemic control and micro vascular complications [15,16,].In this study, it is found that the diabetic retinopathy was 6 % (Proliferative DR was 4.7%, while non proliferative DR was 1.3%), which is lower than that reported in Sjolie AK et al 46%[17], Nguyen TT et al (42%),[18] , Al- Maskari F et al (19%)[19], and Al- Khaldi YM (11.6%)[20].The substantial heterogeneity in reported prevalence of retinopathy may be real to some extent. This may be due to differences in the age distribution of different populations, but may also be due to differences in study methodology and population sampling. The lower percentage of diabetic retinopathy may be due to the fact that we depend on ophthalmoscopic examination only for detection of DR without the use of fundal photography and/or fluorescein angiography, as it is recommended in the screening guidelines which may detect more cases [1]. In this study cataract was present in 10% of patients, which agree with Falck A, et al[21] and higher than 5% reported by Alemazadeh R ,Ali O[1].This may be due to long standing hyperglycemia, and to the fact that it needs less time to develop. In this study, the age of all diabetic patients who had eye complications were more than 10 years , which was the same as the Romero-Aroca P, et al study [22], which assume that the most important risk factor is the pre-pubertal age at onset, and Porta

M, et al study [23] , which thought that sight – threatening retinopathy is rarely reached during pediatric age group, if anything develop takes many years to develop , they suggested that the pre-pubertal years protecting against DRP and it contributed to be an independent risk factor for the development of DRP, but lower than that found in Sjolie AK, et al study [17],and Hietala K, et al study [24]. In this study, there was significant correlation between incidence of eye complications of diabetes and duration of diabetes,which is agree with that reported by Mohamed F El-Bab et al [25],who found that diabetic retinopathy increases with patient age and disease duration; and also with that reported by Verdaguer J et al[26].but lower than Sjolie AK et al study [17], in which the mean duration of diabetes was 14.7 years . Duration of diabetes is known to reflect total glycemic control and risk factor exposure over time[27]. A longitudinal study of Wang S, et al [28], showed that nearly all type 1 diabetics develop retinopathy after a disease duration of 20 years, regardless of their diabetic control. In this study, the eye complications were more in female (14.7%) than male (1.3 %) which is highly significant, it is similar to Mohamed F El-Bab et al [25], who found that women had significantly higher rates of diabetic retinopathy than men, while it is disagree with Araki A et al in which there was no significant differences in diabetic retinopathy according to gender [29]. Also it is different from that found in Sjolie AK et al[17],where female 48.7% while male 51.3 %. In this study, there was no significant association between eye complications and degree of glycemic control, although 17/24 (70.8%) of those with eye complications had Hb1Ac >10. It is different from Romero-Aroca P[22], Romero P[30] , Porta M [23],Sjolie AK [17], Mohamed F El-Bab [25], Rani PK[31], who showed that glycemic control well correlated with retinopathy, and from Karavanaki K[32],Olsen B, et al[33], who observed that the risk of diabetic retinopathy increases with poor glycemic control as compared to other micro vascular complications. Our findings may be due to the fact that we depend on few and sometimes single HbA1c readings in assessing the glycemic control and different sample size studied.

In this study out of 24 patient with eye complication (33.3%) patients had macroalbuminuria which is similar to the Romero P , et al [30], and Sjolie AK, et al [17],who showed that macroalbuminuria correlated well with sever forms of diabetic retinopathy.

In this study, there was significant correlation between presence of limited joint mobility (LJM) and eye complications ,which is similar to Frost D, et al[34].The syndrome of limited joint mobility is frequently associated with the early development of diabetic micro vascular complications, such as retinopathy and nephropathy, which may appear before 18 yr of age [1] , and Limited joint mobility as well as other micro vascular complications (ie, retinopathy and nephropathy) associated with poor glycemic control [35], but it is different from that found in Arkkila PE, et al[36],who found that LJM did not predict diabetic micro vascular complications or vice versa. In this study 16/24 (66.7%) patients with eye complications had short stature which is higher than 5% reported by Simsek DG et al [37], this difference may be due to different size of samples included in the study or to poor control of diabetes of our patients as most children with type 1 diabetes grow normally, however poor glycemic control can result in poor linear growth, and/or delayed skeletal and pubertal development. Therefore height should be monitored carefully at least twice a year and plotted on growth curves, so that deviations can be detected early and therapy appropriately adjusted [38,39].

In this study there was no significant association between the presence of celiac disease (CD) and eye complications, which it is disagree with MollazadeqanK ,et al study[40],who found that the duration of celiac disease correlated with the risk of DRP as individuals with Type1Diabetes and Celiac Disease were at a lower risk of DRP in the first 5 years after Celiac Disease diagnosis and having a diagnosis of Celiac Disease for >10 years is a risk factor for the development of DRP in Type1Diabete mellitus thus long-standing Celiac Disease in patients with type 1DM merits intense monitoring for DRP.

CONCLUSION :

The incidence of eye complications increases with increasing age and duration of diabetes and it is more common in female, the development of cataract is more than diabetic retinopathy,presence of eye complications associated with presence of other chronic complications; diabetic nephropathy and short stature, and that the presence of limited joint mobility correlate with presence of eye complications.

RECOMMENDATIONS :

Screening all patients with type 1diabetes mellitus according to the guide lines is required for early detection and treatment of eye complications, using new methods apart from slit lamp and ophthalmological examination like fundal photography and/or Fluorescein angiography is indicated to detect early changes of diabetic retinopathy, better glycemic control is required for prevention of development eye complications, and the use of Limited Joint Mobility as clinical test for early screening regarding micro vascular involvement including diabetic retinopathy.

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