Original Article

Evaluation of Eye Health in Children with Type 1 Diabetes Mellitus and Celiac Disease

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Abstract

Background: Pediatric celiac disease (CeD) and type 1 diabetes mellitus (T1DM) have well established effects on eye health but comorbid effect is not known. **Aim:** To evaluate the eye health of children with T1DM and CeD to predict microvascular retinal pathologies by diagnosis of probable intraocular pressure increase which is an important glaucoma trigger. **Patients and Methods:** In this case-controlled study, 28 eyes of 14 children both T1DM and CeD, with a mean age of 12.6 ± 3.9 years, and 28 eyes of gender-matched 14 healthy children as a control group were included. In both groups, detailed ocular examinations and measurement of intraocular pressure (IOP), ocular pulse amplitude (OPA), thicknesses of ganglion cell layer (GCL), inner plexiform layer (IPL), retinal nerve fiber layer (RNFL), and choroid thicknesses (CT) were done. All the patients with T1DM and CeD were newly diagnosed. The evaluations of IOP and OPA were made using a Pascal dynamic tonometer and thicknesses measured by optical coherence tomography. **Results:** The IOP and OPA values of the patient group were found to be statistically significantly higher than those of the control group (17.1 and 1.86 vs 14.78 and 1.57 mmHg, P <.0001, P <.001, respectively). IOP values of all patients were higher than IOP cut off levels for diagnosis of hypertension. CT was significantly thinner in the patient group than in the control group (385.4 μm vs 331.71 μm, respectively, P < 0.03). No significant difference was found between the groups in respect of GCL, IPL, and RNFL values. **Conclusion:** The higher IOP and OPA values of the children with T1DM and CeD were considered to be the result of the microvascular pathologies in T1DM and increased inflammation associated with CeD. High IOP and OPA values can lead to damage in the eye as intraocular blood flow and choroidal perfusion are affected. In order to prevent these eye problems, measurement of IOP and OPA should be done in children with diagnosis of T1DM and CeD and also follow up studies needed.

Keywords: *Celiac disease, children, choroid thickness, eye, glaucoma, intraocular pressure, ocular pulse amplitude, type 1 diabetes mellitus*

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Introduction

Many systemic diseases may effect eye health with different mechanisms.[1-5] Type 1 diabetes mellitus (T1DM) has well established microvascular and autonomic complications on eye health. Autoimmunity plays a role in T1DM and also in celiac disease (CeD).[6] CeD eye manifestation is connected to malabsorption and low levels of calcium, vitamin D, and vitamin A. These minerals and vitamins are important for eye health, and severe deficiency can lead to dry eye as well as cataracts. Other celiac eye

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issues are autoimmune disorders due to brain occipital calcification and orbitopathy; eye inflammation, uveitis, and orbital myositis.[7] The link between celiac disease and type 1 diabetes is not well-documented. In the T1DM patients, the risk of comorbid CeD development risk is 4–9%.[6] The detection of these microvascular complications needs careful examination of an anterior and posterior segment of the eye.

The vascular choroid lines the posterior eye and has a range of important and diverse anatomic and physiologic roles including supplying the outer retina with oxygen and nutrients, ocular temperature regulation, the regulation of intraocular pressure (IOP), and the absorption of light.[8]

IOP variations may damage the optic nerve head. A high pressure-induced deformation of the lamina cribrosa eventually triggers the dysfunction and death of the retinal ganglion cell axons.[9] IOP increase leads to glaucoma which is third most common cause of severe visual impairment and blindness in children especially in underdeveloped areas of the world and responsible 5% of blindness globally.[10]

The measurement of IOP and ocular pulse amplitude (OPA) is a current method used to show hemodynamic changes in the eye. Pascal dynamic contour tonometer is a non-invasive method which is accepted as the gold standard in IOP measurement.[11]

Decreased endothelial cell density, choroidal thinning and increased choroidal thickness (CT) were reported in pediatric T1DM while a decrease in thickness of retinal nerve fiber layer, and decrease in CT in patients with pediatric CeD are reported findings.[1-5,12]

There is no information in literature related with eye health in children with T1DM and also CeD. The primary objective of this study is to investigate the effect of pediatric T1DM and CeD on eye health findings by detailed examination of anterior and posterior segment of the eye, vision screening, measurement of IOP, OPA, CT, the retinal nerve fiber layer (RNFL), and internal plexiform layer (IPL), and the secondary objective is to detect the intraocular hypertension early since IOP is a glaucoma triggering condition.[13]

Materials and Methods

Clinical setting

The prospective case control study was carried out in a tertiary hospital with 34,000 pediatric admissions per year. According to files of pediatric gastroenterology department, 14 out 272 CeD patients were diagnosed with T1DM as a comorbid disease.

Children diagnosed as T1DM were admitted to the hospital with either diabetic ketoacidosis or symptoms of diabetes. Diagnosis of T1DM made by using blood glucose monitoring, diabetes autoantibodies, and glycosylated hemoglobin (HbA1c) value according to criteria determined by the International Society for Pediatric and Adolescent Diabetes.[14] The T1DM patients followed in the department of pediatric endocrinology by the resident pediatric endocrinology specialist who took care of the child. Patients with T1DM who were found to have positive tissue transglutaminase IgA antibodies at the screening via celiac disease antibodies at the time of diagnosis were referred to pediatric gastroenterology department. Definitive diagnosis of CeD made according to European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic criteria by pathology results of biopsy material taken from the duodenum.[15]

After diagnosis, age appropriate T1DM and CeD treatments were started, and the patients were followed up at both departments with control tests and regular visits. Twenty-eight eyes of these 14 patients with T1DM and CeD formed the patient group (11 years, 4–18; mean; min–max). Diagnosis of CeD were made at the same time of T1DM diagnosis and mean duration of follow up were one month for CeD patients and T1DM diagnosis and follow up duration were also about one month.

Control group consists of 28 eyes of 14 healthy children in the same age who admit for routine health screening in the department of general pediatrics. All children were examined by the same pediatric specialist (AA) with the same set of laboratory tests. The children with any systemic disease that eye could be involved or eye/retinal disease excluded from group.

Arterial blood pressure measurements were made and blood tests were evaluated for all the patient and control group subjects recorded. Blood tests including hemoglobin, iron, vitamin D, vitamin B12, C-reactive protein, and erythrocyte sedimentation rate were in the normal range in both groups.

Arterial blood pressure measurements were made by medical devices (WelchAllyn, Taiwan) from the right arm with six measurements one minute apart after a 15 minutes resting and mean of these measurements taken into consideration. Age and weight appropriate instruments were used for measurements. Percentiles of systolic and diastolic blood pressure measurement results were calculated using both (the National Institute of Health's National Heart, Lung, and Blood Institute)

NIH/NHLBI (2004) and the (American Academy of Pediatrics) AAP (2017) guidelines.[16]

Exclusion criteria

All the children controlled for other diseases leading to eye or retinal diseases by the use of biochemical and other laboratory tests. Except T1DM and CeD diseases, any condition or disease that would be leading to eye or retinal problem excluded from the study group.

Exclusion criteria were defined as presence of metabolic unstably, corneal abnormality, intraocular pressure greater than 21 mmHg, retinal disease, glaucoma, strabismus, optic disc disorders history of surgery or trauma related to eye, refraction error greater than ± 3 diopters, any comorbid systemic disease other than CeD or T1DM, children less than 4 years of age who were unable to adapt to optical coherence tomography, patients using medications regularly for different diagnosis, the patients who were not following the gluten free diet.

Eye Examination

Detailed vision screening via eye examination (standard slit-lamp examination, refractive error evaluation and best-corrected visual acuity determination, detailed fundoscopy, and perimetry) made by resident ophthalmology specialist. And IOP and OPA values were measured using Pascal dynamic contour tonometer, GCL, IPL, RNFL, and CT values were measured by ED imaging Optical coherence tomography in ophthalmology department by the same specialist who were blinded about the groups of children.

Pascal dynamic contour tonometer

Pascal dynamic contour tonometer (Swiss Microtechnology AG, Port, Switzerland) is accepted as the gold standard in IOP measurement since it is not effected from corneal thickness and corneal elasticity. It is a non invasive method which obtains IOP value by adding a slit lamp to a contact tonometer. OPA reflects blood flow of the eye corresponding to each heartbeat and choroid perfusion indirectly.[17]

The mean of three consecutive intraocular pressure readings was calculated for each eye. All the measurements were performed between 09.00 and 12.00 am hours to avoid any effect of diurnal rhythm effect on ocular pulse amplitude. The accuracy of each measurement was assessed using a qualitative score provided by the device, and intraocular pressure readings were included only if their Q values were between 1 and 3 (Q = 1 optimum; Q = 2 or 3 acceptable; Q = 4 questionable; Q = 5 or 6 repetition recommended).

Optical coherence tomography measurement

Enhanced depth imaging optical coherence tomography (Spectralis optical coherence tomography®; Heidelberg Engineering, Heidelberg, Germany) is a currently used convenient non invasive and non contact technique and can yield images similar to biopsy material viewed under a microscope. This provides deeper cross-sectional information about the choriocapillaris, CT, the retinal nerve fiber layer (RNFL), and internal plexiform (IPL) layer that can provide early information about initial signs of systemic diseases which lead to metabolic stress.[18]

The measurements of choroid and GCC complex thicknesses were performed by using optical coherence tomography without pupil dilatation by a trained optical coherence tomography technician using a spectral domain-optical coherence tomography device. Optical coherence tomography calculates delays in reflected light in different layers of the eye, allowing the reflected light to be converted into 3D images showing depth dimensions. All optical coherence tomography measurements were performed at certain hours (between 09:00 a.m. and 12:00 a.m.) to avoid any diurnal variation effect. About 9 mm high-resolution line scan passing the horizontal fovea was recorded using the integral software on the device (Heidelberg Eye Explorer®, Version 1.7.0.0; Heidelberg Engineering). RNFL, GCL, IPL, and CT were measured using the new spectralis segmentation software. Manual measurements of the CT were done by the same resident ophthalmology specialist based on the distance between the hyporeflective line, representing the sclerochoroidal interface and the pigment epithelium, which is represented by the outer edge of the hyper-reflective line. The average of three measurements taken from the subfoveal area and two other patients at 500μ distance of the nasal and temporal parts of the fovea was calculated.

Statistical analysis

SPSS®, Version 21, software (Chicago, IL, USA) was used to perform statistical analysis. Central and prevalence criteria, such as number, percentage, mean, and standard deviation were used to create descriptive statistics. The compatibility of the numerical variables to a normal distribution was evaluated both visually (histogram) and analytically (the Shapiro–Wilk test, Skewness and Kurtosis) according to the numerical values, P <.05 was regarded as statistically significant in all tests. The results of the histograms, the Shapiro–Wilk tests and ranges of Skeewness and Kurtosis indicated that the data had normal distribution, therefore, independent samples t-tests were used to determine the differences between the groups.

Results

The study group comprised of 8 (57.1%) females and 6 (42.9%) males with a mean age of 12.6 ± 10.6 years. The control group comprised of 8 (57.1%) females and 6 (42.9%) males with a mean age of 13.7 ± 15.9 years. Mean age and gender ratio of groups were similar statistically ($p > 0.05$). Systolic and diastolic pressure measurement results were in normal range for age in both groups. Blood tests including hemoglobin, C-reactive protein, erythrocyte sedimentation rate, iron, vitamin D, and vitamin B12 were in the normal range in both groups.

The vision screening results and ocular examinations were normal in both groups. The IOP and OPA values of the patient group (T1DM and CeD) were significantly higher than those of the control group [17.1 and 1.86 vs 14.78 and 1.57 mmHg, $P < 0.0001$, $P < 0.001$, respectively, Table 1, Figures 1 and 2]. CT was significantly thinner in the patient group than in the control group [385.35 μm vs 331.7 μm, respectively, $P < 0.03$, Figure 3]. No significant difference was found between the groups in respect of GCL, IPL, and RNFL thicknesses values [Table 2].

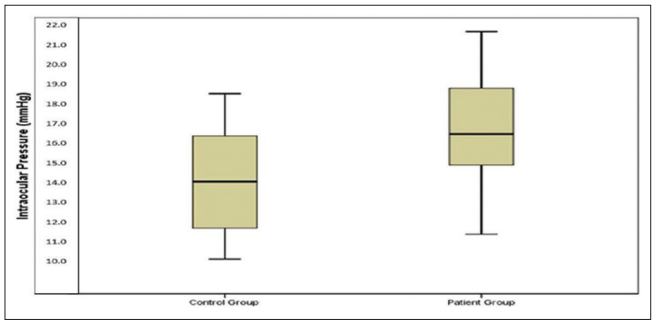

Figure 1: The intraocular pressure values of the patient and the control group

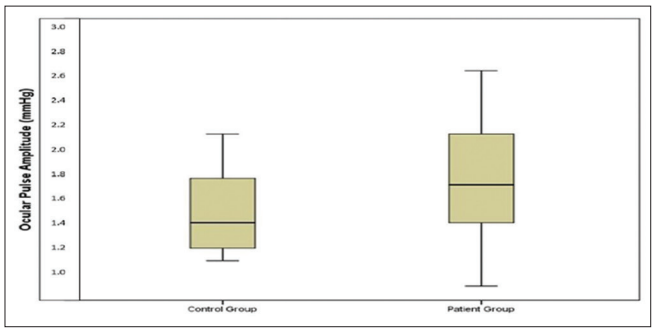

Figure 2: The Ocular pulse amplitude values of the patient and the control group

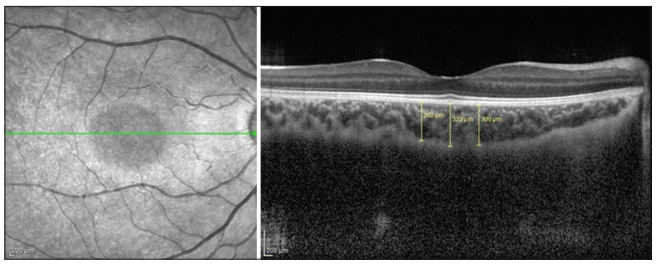

Figure 3: An example of choroid thickness measurement by optical coherence tomography of the patient with type 1 diabetes and celiac disease

Discussion

To the best of our knowledge, this is the first case control prospective study about eye findings performed

Table 1: Intraocular pressure and ocular pulse amplitude measurement results of the patient and control group of eyes

Group	*n*	Mean	SD	*P*
IOP mmHg				
Patient	28	17.10	2.58	0.00
Control	28	14.78	2.54	
OPA mmHg				
Patient	28	1.86	0.47	0.01
Control	28	1.57	0.29	

IOP: Intraocular pressure, OPA: Ocular pulse amplitude

Table 2: Optical coherence tomography measurement results of the patient and control group of eyes

	n	M	SD	*P*
CT μm				
Patient Group	28	331.71	51.15	0.003
Control group	28	385.35		
GCL μm				
Patient Group	28	1.16	0.07	0.89
Control group	28	1.17		
IPL μm				
Patient Group	28	0.94	0.05	0.95
Control group	28	0.94		
SRNFL μm				
Patient Group	28	126.82	17.33	0.82
Control group	28	127.86		
NRNFL μm				
Patient Group	28	75.18	10.22	0.16
Control group	28	79.86		
IRNFL μm				
Patient Group	28	131.32	13.70	0.36
Control group	28	135.04		
TRNFL μm				
Control Group	28	74.61	10.41	0.80
Control group	28	73.89		
GRNFL μm				
Patient Group	28	102.04	8.32	0.38
Control group	28	104.18		

CT: Choroid thickness, GCL: Ganglion cell layer, IPL: Inner plexiform layer, SRNFL: Superior retinal nerve fiber layer, NRNFL: Nasal retinal nerve fiber layer, IRFNL: Inferior retinal nerve fiber layer, TRNFL: Temporal retinal nerve fiber layer, GRNFL: Global retinal nerve fiber layer

in pediatric age group with both T1DM and CeD in the literature. The results of this pediatric study showed that mean of the IOP and OPA measurements of patients with newly diagnosed T1DM and CeD were higher than those of the control group. This high IOP measurement results of every patient were higher than the limits for diagnosis of intraocular hypertension for age.[19] Our study results revealed that development of T1DM in pediatric CeD patients leads to important changes in retinal vascular tension that reflected as intraocular hypertension. Optic nerve damage due to retinal vein occlusion and decreased choroidal thickness after development of intraocular hypertension in a child is important since it may lead to glaucoma and vision loss in long-term follow-up.[20-23] If diagnosed early enough, intraocular hypertension treatment is possible and these complications can be prevented.[13]

This is the first study supporting early screening for IOP and OPA in all pediatric patients with T1DM and CeD. In order to prevent irreversible eye pathologies like glaucoma and keep the child engaged to proper academic potential and sports with healthy eyes, this screening should be recommended for all pediatric patients with T1DM and CeD at the time of diagnosis.[20,24]

The underlying mechanisms linking diabetes and elevated IOP have not been fully elucidated. T1DM disease leads to microvascular damage, corneal damage, and choroid inflammation. Accumulating evidence suggests that a hyperglycemic status may disrupt cell and repair functions in the cornea and potentially affect the central corneal thickness.[25,26]

But this effect is time dependent and is expected to develop in a relatively long time. In pediatric T1DM study by Ducic *et al*.,[22] the risk of severe eye complications increases with the duration of diabetes leading to complications after 10 years duration. And in the series of Krolewsky *et al*.,[27] the risk of development of severe eye complications was almost nonexistent during the first 10 years of diabetes, but rose to its maximum level, and remained at that level for the next 25 years. Our findings were also consistent with these literature data because we did not find any retinal damage findings in OCT.

In our patients, intraocular hypertension diagnosis was made at the same time along with the diagnosis of T1DM and CeD. Although T1DM is newly diagnosed, the high IOP of pediatric patients may be associated with CeD that is characterized by auto antibodies toward gluten that cause multisystemic autoimmune tissue damage especially in intestines and other tissues such as ear and brain.[28]

In literature, there are two adult studies in CeD patients reporting no increase in intraocular pressure but there is no information about children with CeD.[29,30] In the study of Schmidt *et al*.,[31] there was no IOP difference in adult DM patients without retinopathy compared to the control group. Pekel E *et al*.[32] reported that there are no statistically significant differences between the pediatric diabetic patients and healthy controls in terms of IOP. Other pediatric study reported no difference in IOP in children with DM without retinopathy but found high IOP measurement in group with retinopathy. Although the IOP measurement techniques and patient group of Blanksma *et al*.[33] were different from ours, high IOP in our patient group would be related with diagnosis of CeD in our T1DM patients. The role of CeD in developing intraocular pressure is not clear. Further studies in T1DM and CeD pediatric patients with higher number and long-term follow-up needed.

The results of our study showed that the CT of the patient group without retinopathy were thinner compared to the control group. Ermerak BC *et al*.[34] demonstrated the evidence of peripapillary choroidal thinning in pediatric diabetic patients without visible signs of retinopathy. In our previous study with pediatric CeD, we also had found thinning at subfoveal, nasal, and temporal areas of choroid even after 1 year of diagnosis and gluten-free diet.[35] Dogan *et al*.[2] found an insignificant decrease at subfoveal area in pediatric CD patients at gluten free diet for 5 years.

In our study, there was no significant difference between means of the GCL, IPL, and RNFL measurements between the groups. In our previous study, we had found that RNFL, GCL, and IPL measurement mean results in pediatric CeD patients were similar to the control group also.[35] But Karatepe Hashas AS *et al*.[1] reported a decrease in global, temporal, superior temporal, and superior nasal RNFL thicknesses in pediatric CeD group. But in that study the mean follow up duration was 5 years. Other T1DM study by Pekel E *et al*.[32] revealed that in T1DM pediatric patients there were no change in RNFL, GCL, and IPL thicknesses too. Karti O *et al*.[36] reported that in children with T1DM GCL-IPL thickness which reflects early neurodegenerative effect of T1DM is thinner, but the RNFL thickness was not significantly decreased. Our study results may be reflecting very early stage of pathogenesis of retinal injury in pediatric patients with T1DM and CeD since our patients were newly diagnosed.

Limitations of the study

We could not be able to compare our results with literature in discussion in detail because there was no study in literature giving the ocular findings of pediatric

CeD and T1DM together. Related eye literature stated that early detection would prevent vision problems if early treatment started. Our study does not include a patient group with only diagnosis of CeD and T1DM in order to compare the pure effects pediatric CeD and T1DM effect on IOP and OPA.

Conclusions

In conclusion, this study demonstrated that pediatric patients newly diagnosed with both T1DM and CeD has higher IOP and OPA values than the control group. These increases in IOP and OPA measurements of the children with T1DM and CeD were considered to be the result of the microvascular pathologies in T1DM and increased inflammation associated with CeD. High IOP and OPA values would damage the eye as increase in intraocular blood flow and choroidal perfusion. In order to prevent these eye problems, early measurement of IOP and OPA should be recommended in children with T1DM and CeD at the time of diagnosis and also follow-up of those measurements needed. Even routine ocular examination reveals no abnormality for the early determination of ocular damage and prevents progressive optic nerve damage; for screening purposes, the non-invasive method of dynamic tonometer should be used in this group of pediatric patients who are diagnosed with both T1DM and CeD.

Authors' contribution

Author SD and author AA have given substantial contributions to the conception or the design of the manuscript, author ID, author SB and author ASK to acquisition, analysis and interpretation of the data. All authors have participated in drafting the manuscript; author ŞH revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript, read, and approved the final version of the manuscript.

Ethical statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Adıyaman University Ethics Committee (2020/1-3). The necessary approvals were obtained from the provincial directorate of national education to which the study schools were affiliated. Written informed consent was obtained from both parents and children.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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