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Differences in corneal and anterior segment morphology between diabetic *vs.* healthy children and adolescents: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: To compare corneal and anterior segment morphology among children and adolescents with and without diabetes.

MATERIALS AND METHODS: PubMed, Embase and Scopus databases were systematically searched. Studies that were observational in design were considered. Included studies should have been done in young children and/or adolescents and compared relevant outcomes of interest based on the diabetic status. The outcomes of interest were related to corneal morphology, morphology of lens, as well as important characteristics of anterior segment such as depth, pupillary diameter, intra-ocular pressure and axial length. The pooled effect sizes were reported as weighted mean difference (WMD). STATA software was used for statistical analysis.

RESULTS: The meta-analysis included 17 studies. Diabetic children had lower corneal endothelial cell density (cells/mm^2) (WMD -215.7, 95% CI: -406.5, -24.9), higher central corneal thickness (μm) (WMD 12.66, 95% CI: 5.47, 19.84), higher lenticular thickness (mm) (WMD 0.25, 95% CI: 0.13, 0.36) and density (WMD 3.02, 95% CI: 2.23, 3.81) than non-diabetic children. The anterior chamber depth (mm) (WMD -0.17, 95% CI: -0.24, -0.09) and pupillary diameter (mm) (WMD -0.61, 95% CI: -1.12, -0.10) was significantly reduced in diabetic children, compared to non-diabetic children. No differences in the corneal curvature, corneal diameter, spherical equivalent, intra-ocular pressure, axial length, tear film breakup time and Schirmer test were noted among diabetic and non-diabetic children.

CONCLUSIONS: Significant structural changes in cornea and lens along with reduction in anterior chamber depth and pupillary diameter were found. These morphological changes may be indication for early and prompt management and underscore the need for more advanced ophthalmological evaluation techniques, in addition to routine examination.

Key Words:

Anterior segment, Corneal morphology, Lens morphology, Children, Adolescents, Type 1 diabetes, Meta-analysis.

Introduction

There has been an increasing global burden of diabetes mellitus (DM). Findings of the Global Burden of Disease Study (2017) suggest that the worldwide prevalence is around 475 million and this is projected to increase to around 570 million by the year 2025[1]. Further, the disability adjusted life year (DALYs) due to diabetes is expected to increase by around 15% i.e., from nearly 68 million in 2017 to 80 million in 2025[1]. Another review by Saeedi et al[2] estimated the global prevalence of diabetes to be around 9% in the year 2019 and further suggested that will would increase to around 11% by the year 2045. This increasing burden of DM in also expected to be seen in children and adolescents. An increasingly lower age of onset of diabetes is documented in some of the recent studies[3,4].

One of the commonest chronic diseases in children is the Type 1 DM which is the consequence of destruction of pancreatic beta cells that produce insulin[5]. This results in insulin deficiency and imbalances in glucose metabolism. According to the International Diabetes Federation report (2017), over a million children and adolescents are likely to have been diagnosed with Type 1 DM[6]. The global pooled incidence of Type 1 DM among children has been documented to be nearly 11 per 1,00,000 child years[7]. The review also found an increasing trend in the incidence i.e., an incidence of 10 per 100000 child years in 1990-1999 to 21 per 100000 child years in 2010-2015[7]. A review by Lawrence et al[8] documented that a 45% relative increase in the prevalence of type 1 diabetes and >90% relative increase in the prevalence of type 2 DM among children and adolescents in the United States from the year 2001 to 2017. A multicentre prospective study from 26 European countries noted an approximately 3.5% annual increase in the incidence of childhood diabetes from the year 1989 to 2013[9].

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It is well known that diabetes impacts the overall health and increases the risk adverse events. It has a negative impact on the vascular systems and therefore leads to varied health outcomes such as cardiovascular disease/ischemic heart disease, cerebrovascular disease and peripheral vascular disease because of its effect on microvasculature[10-12]. Due to diabetes associated microvascular pathology, there is also an increased risk of neuropathy, retinopathy and nephropathy[12-14]. Of particular interest are the ocular complications as they are progressive and one of the emerging causes of substantial morbidity globally. This is also important as early detection and management could stagger the progress and prevent severe ocular complications[15]. Hyperglycaemia in diabetes triggers a whole cascade of inflammatory events and endothelial dysfunction and leads to severe complications such as retinopathy, optic neuropathy, cataract, error in refraction, glaucoma, other ocular surface diseases such as dry eye and corneal diseases and in severe cases, partial or complete visual loss[16,17].

There are ample studies[18-21] looking at the effect of diabetes in adults on ocular complications, both the anterior and posterior segment. Most of the studies[22-24], in relation to diabetes, in children are focused on studying posterior segment clinical conditions such as diabetic retinopathy. Diabetes is also a significant risk factor for progressive damage to the cornea, lens and other anterior segment structures[25,26]. There are studies[26,27] that suggest that diabetes leads to a decrease in nerve density within cornea and also reduces corneal sensitivity. This could lead to repeated epithelial disruption, corneal ulceration and possibly, vision impairment. However, these anterior segment complications are not well acknowledged by health care providers. With the increasing burden of diabetes in children and adolescents, it is important to carefully understand the impact of diabetes on morphology of anterior segment structures. Such an understanding is critical to identification, management, and prevention of ocular morbidities in children at a very early stage. With these considerations, the current meta-analysis was planned to compare and document the differences between corneal and anterior segment morphology among diabetic children and their healthy counterparts.

Materials and Methods

Search Strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were adhered to during the conduct of this meta-analysis[28]. The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO, No. CRD42022297046). PubMed, Embase and Scopus databases were used for a thorough systematic search of English language papers published until 10th December 2021. The search strategy included the use of medical subject heading (MeSH) terminology, as well as free text words. The search strategy incorporated the following: (diabetes OR high blood sugar OR hyperglycemia OR diabetic) AND (child OR children OR young children OR adolescent) AND (anterior chamber morphology OR iris OR pupil OR lens OR cornea OR corneal thickness OR anterior chamber depth OR lens thickness OR lens morphology OR corneal morphology OR pupillary diameter).

The literature search aimed at identifying studies that compared the relevant outcomes among children based on their diabetic status i.e., children with diabetes compared to non-diabetic normal children. The outcomes of interest were related to corneal morphology (central corneal thickness, diameter, curvature and endothelial cell density), morphology of lens (thickness, density and spherical equivalent), as well as important characteristics of anterior segment such as depth, pupillary diameter, intra-ocular pressure and axial length. It is important to mention that as part of this review, the focus was on anatomical/morphological characteristics and not the functional and/or physiological aspects of the anterior segment. Further, the review was focused only on the anterior segment of the eye.

Selection Criteria and Methods

Upon identification of studies on literature search and removal of the duplicates, two subject experts from the team reviewed the studies, screened the titles and abstracts as the initial step. The full text of possible studies was subsequently reviewed. Any disagreements in the inclusion of the studies were resolved through discussions between the study authors. In order to identify additional literature, the reference list of the included studies was also reviewed.

Inclusion Criteria

Studies that were observational in design were considered for inclusion. Studies eligible for inclusion should have been done in young children and/or adolescents and had compared relevant outcomes of interest based on the diabetic status (diabetic or not diabetic) of the included children.

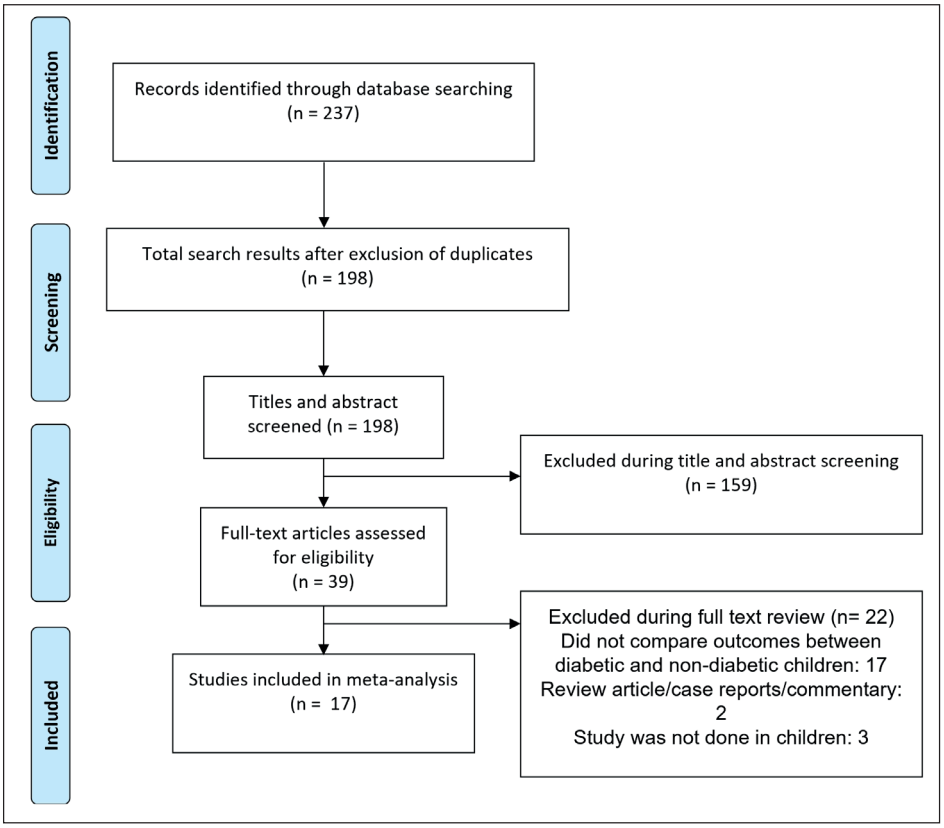

Figure 1. Selection process of the studies included in the review.

Exclusion Criteria

Case-reports or review articles were excluded. Studies that were conducted in adults/older population or did not provide comparative findings based on the diabetic status of the children were excluded. Also, studies that reported on the outcomes related to posterior segment of the eye were also not considered.

Data Extraction and Quality Assessment

Through use of a pretested data extraction sheet, two authors (YG and YY) separately extracted data from the included studies. Data extracted mainly included the study identifier i.e., the name of the first author along with the year of publication; study setting and design, participant characteristics, sample size and the key findings. The quality assessment of the included studies was done independently by two authors using the Newcastle-Ottawa Quality Assessment Scale for observational studies[29].

Statistical Analysis

For all the analysis, STATA version 16.0 was used. The pooled effect sizes were reported as weighted mean difference (WMD). All effect sizes were reported along with 95% confidence intervals (CI). I^2 was used as a measure to denote heterogeneity and in instances where the value of I^2 exceeded 40%, random effects model was used[30]. A *p*-value of less than 0.05 was considered for statistical significance.

Results

Selection of Articles, Study Characteristics and Quality of Included Studies

Using the search strategy in the databases, a total of 237 citations were obtained. After removal of the duplicates, overall, 198 relevant citations were obtained (Figure 1). Screening of the titles and abstracts led to removal of 159 citations. Out of the remaining, 22 studies were excluded after reading the full text. Finally, a total of 17 studies[31-47] were considered for the inclusion. Table I presents the details of the studies included in the review. All of the included studies were observational in design with majority being cross-sectional in nature. Most studies were conducted in Turkey (n=9) [31,34,36,41,43-47]. Three studies[32,33,42] were done in Poland and two[39,40] in China. One study each was done in India, Romania and Egypt[35,37,38]. All the studies included

Table I. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM *vs.* no DM)
Ozturk et al[31] (2020)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); male (52.1%); mean age of 13.5 years; Mean Tanner puberty stage of 3.3 (1.4); average age of DM onset: 6.8 (1.5) years; average duration of DM: 6.7 (1.4) years; no difference in two groups for blood pressure, high density lipoprotein (HDL); low density lipoprotein (LDL) and triglyceride levels	DM-70; no DM-72	Axial length (mm) (mean, SD): 22.69 (0.33); 22.7 (0.22) Central corneal thickness (µm) (mean, SD): 551.3 (18.0); 546.2 (13.5) Anterior chamber depth (mm) (mean, SD): 3.50 (0.12); 3.67 (0.11) Lens thickness (mm) (mean, SD): 3.65 (0.15); 3.37 (0.14) Corneal curvature (Dioptre) (mean, SD): 42.77 (1.50); 42.81 (1.20) Spherical equivalent (Dioptre) (mean, SD): 0.33 (0.70); 0.37 (0.74) Tear film breakup time (TBUT) (Sec) (mean, SD): 14.5 (2.0); 14.7 (2.0) Schirmer test (mm) (mean, SD): 15.2 (2.1); 15.6 (1.9) Intra-ocular pressure (mean, SD): 15.1 (2.2); 14.9 (2.2)
Jeziorny et al[32] (2019)	Cross-sectional	Poland	Children with type 1 diabetes mellitus (DM); female (48.4%); median age of 12.4 years; median duration of DM: 4.6 years; median BMI of 19.5 kg/m^2	DM-119; no DM-38	Central corneal thickness (µm) (mean, SD): 578.8 (34.97); 565.3 (31.5)
Jeziorny et al[33] (2018)	Cross-sectional	Poland	Children with type 1 diabetes mellitus (DM); Diabetic subjects were majorly female (57%) with a median age of 13.2 years (age range of 8-18 years); median duration of DM: 5.5 years; Control group subjects had a median age of 13.3 years (age range of 6-18 years) and majority were males (72%)	DM-54; no DM-40	Central corneal thickness (µm) (mean, SD): 580 (11.5); 566 (12.25)
Akinci et al[34] (2009)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 13.2 years; Control group subjects had a mean age of 10.3 years	DM-59; no DM-38	Central corneal thickness (µm) (mean, SD): 576.9 (41.8); 521 (16.6)
Fernandes et al[35](2019)	Cross-sectional	India	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 12.16 years and females were 52%; Control group subjects had a mean age of 12.3 years and females were 44%; mean duration of diabetes was 3.9 years	DM-50; no DM-50	Central corneal thickness (µm) (mean, SD): 525.2 (33.1); 513.4 (29.5) Endothelial cell density (cells/mm^2) (mean, SD): 3039.6 (292.8); 3360.4 (268.0)
Akil et al[36] (2016)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 13.2 years and females were 52.4%; Control group subjects had a mean age of 13.3 years and females were 50%; mean duration of diabetes was 3.6 years	DM-42; no DM-42	Central corneal thickness (µm) (mean, SD): 555.4 (41.2); 561.5 (39.7) Tear film breakup time (TBUT) (Sec) (mean, SD): 13.3 (3.27); 12.1 (1.76) Schirmer test (mm) (mean, SD): 15.5 (3.94); 20.9 (3.81) Intra-ocular pressure (mean, SD): 16.7 (2.9); 14.7 (2.55)
Tiutiuca et al[37] (2013)	Cross-sectional	Romania	Children with type 1 diabetes mellitus (DM); corneal thickness measured using TOPCON TRK-1P auto-refracto-kerato-tonometer.	DM-100; no DM-100	Central corneal thickness (µm) (mean, SD): 541.1 (30.9); 538.3 (32.8)
Anbar et al[38] (2016)	Cross-sectional	Egypt	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 8.22 years, females were 60% and mean BMI was 17.2 kg/m2; Control group subjects had a mean age of 7.83 years, females were 65% and mean BMI was 17.6 Kg/m^2; mean duration of diabetes was 3.51 years	DM-80; no DM-40	Central corneal thickness (µm) (mean, SD): 537 (33.4); 504.7 (23.9) Endothelial cell density (cells/mm^2) (mean, SD): 3149.8 (343.7); 3308.8 (99.3)
Wang et al[39] (2019)	Case-control	China	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 10.0 years, females were 54% and mean BMI was 17.7 kg/m2; Control group subjects had a mean age of 9.43 years, females were 52% and mean BMI was 17.1 Kg/m^2	DM-50; no DM-46	Central corneal thickness (µm) (mean, SD): 562.3 (28.5); 573.4 (32.9) Corneal curvature (Dioptre) (mean, SD): 43.1 (1.86); 43.3 (1.68) Intra-ocular pressure (mean, SD): 18.2 (3.5); 18.4 (2.6) Pupil diameter (mm) (mean, SD): 5.46 (2.6); 6.48 (2.34) Corneal diameter (mm) (mean, SD): 12.09 (0.41); 11.66 (1.92)

Continued

Table I (Continued). Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics	Sample size	Key outcomes (DM *vs.* no DM)
Xiao et al*[40]*(2019)	Case-control	China	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 10.6 years, females were 53.7%; Control group subjects had a mean age of 9.5 years, females were 49% ; mean duration of diabetes was 4.2 years	DM-54; no DM-53	Central corneal thickness (μm) (mean, SD): 560.3(29.3); 571 (31.6) Corneal curvature (Dioptre) (mean, SD): 43.14 (1.76); 43.2 (1.63) Axial length (mm) (mean, SD): 23.86 (1.36); 24.28 (1.20) Anterior chamber depth (mm) (mean, SD): 3.52 (0.26); 3.72 (0.26) Lens thickness (mm) (mean, SD): 3.49 (0.18); 3.40 (0.16) Spherical equivalent (Dioptre) (mean, SD): -1.13 (2.45); -1.59 (1.96)
Karahan et al*[41] *(2021)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 11.2 years, females were 36.7%; Control group subjects had a mean age of 9.6 years, females were 53.3% ; mean duration of diabetes was 6.3 years	DM-60; no DM-30	Central corneal thickness (μm) (mean, SD): 564.4 (26.5); 534.3 (33.2) Anterior chamber depth (mm) (mean, SD): 3.09 (0.20); 3.10 (0.30) Corneal curvature (Dioptre) (mean, SD): 44.50 (1.68); 44.45 (1.73) Corneal volume (mm^3) (mean, SD): 61.84 (2.9); 59.57 (3.0) Anterior chamber volume (mm^3) (mean, SD): 191.6 (29.9); 191.95 (35.5) Pupil diameter (mm) (mean, SD): 3.81 (0.90); 3.86 (0.60) Endothelial cell density (cells/mm^2) (mean, SD): 3063.5 (281.2); 3083 (303.1) Mean lens density (mean, SD): 8.55 (2.5); 7.76 (0.30) Maximum lens density (mean, SD): 52.6 (25.3); 47.2 (15.6)
Urban et al*[42] *(2013)	Cross-sectional	Poland	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 15.34 years, males were 48.8%; Control group subjects had a mean age of 14.6 years, males were 53.2% ; mean duration of diabetes was 8.02 years	DM-123; no DM-124	Central corneal thickness (μm) (mean, SD): 550 (30); 530 (33) Endothelial cell density (cells/mm^2) (mean, SD): 2435.5 (443.4); 2970.8 (270.1)
Bayat et al*[43] *(2020)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 14.3 years, females were 57%; Control group subjects had a mean age of 13.2 years; mean duration of diabetes was 4.5 years	DM-56; no DM-50	Central corneal thickness (μm) (mean, SD): 556 (30); 536 (36) Endothelial cell density (cells/mm^2) (mean, SD): 2975 (248); 3012 (257) Anterior chamber depth (mm) (mean, SD): 3.69 (0.31); 3.83 (0.27) Iridocorneal angle (mean, SD): 44.1 (6.6); 45.5 (7.3) Corneal curvature (Dioptre) (mean, SD): 42.75 (1.41); 42.37 (1.5) Pupil diameter (mm) (mean, SD): 4.29 (1.2); 5.17 (1.36)
Tekin et al*[44] *(2017)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 13.1 years, males were 50%; Control group subjects had a mean age of 12.2 years; males were 52.9%; mean duration of diabetes was 7.1 years	DM-56; no DM-51	Corneal diameter (mm) (mean, SD): 12.2 (0.9); 12.2 (0.8) Mean lens density (mean, SD): 8.15 (0.41); 7.86 (0.33) Maximum lens density (mean, SD): 35.3 (2.3); 32.3 (1.9) Lens thickness (mm) (mean, SD): 3.53 (0.23); 3.23 (0.19)
Uzel et al*[45] *(2016)	Cross sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 10.9 years, females were 57.4%; Control group subjects had a mean age of 11.6 years; females were 42%; mean duration of diabetes was 4.79 years	DM-47; no DM-50	Axial length (mm) (mean, SD): 22.85 (0.81); 23.23 (1.50) Central corneal thickness (μm) (mean, SD): 542.95 (37.8); 541.38 (36.3) Anterior chamber depth (mm) (mean, SD): 3.11 (0.36); 3.44 (0.31) Lens thickness (mm) (mean, SD): 3.71 (0.41); 3.37 (0.29) Pupil diameter (mm) (mean, SD): 5.90 (1.09); 6.67 (1.31) Spherical equivalent (Dioptre) (mean, SD): 0.57 (0.27); 0.53 (0.23)
Cinici et al*[46] *(2014)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 12.5 years, females were 55.2%; Control group subjects had a mean age of 11.5 years; females were 42.3%; mean duration of diabetes was 4.72 years	DM-49; no DM-46	Central corneal thickness (μm) (mean, SD): 567.38 (33.3); 554.2 (42.8)
Yuksekkaya et al*[47] *(2014)	Cross-sectional	Turkey	Children with type 1 diabetes mellitus (DM); Diabetic subjects had a mean age of 13.1 years, males were 53%; Control group subjects had a mean age of 13.0 years; females were 40.3%; mean duration of diabetes was 5.1 years	DM-66; no DM-72	Central corneal thickness (μm) (mean, SD): 555.2 (38.6); 547.7 (31.5) Intra-ocular pressure (mean, SD): 15.7 (4.0); 15.2 (3.1)

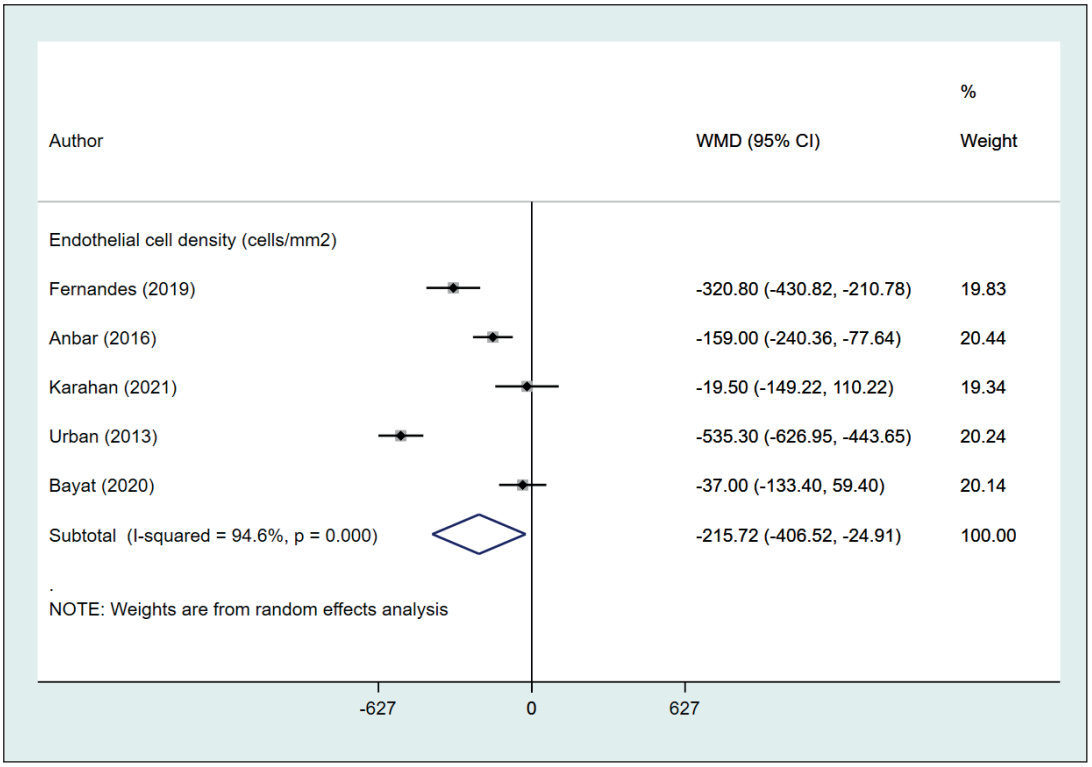

Figure 2. Comparison of corneal endothelial cell density in diabetic children, compared to normal children.

children with type 1 diabetes. The average duration of diabetes in included children ranged from 3.5 to 8.0 years. The results of the quality evaluation of the included studies are provided in **Supplementary Tables I** and **II**. The included studies were of modest to good quality.

Findings Related to Corneal Morphology

In children who were diabetic, compared to non-diabetic children, the endothelial cell density (cells/mm^2) was significantly lesser (WMD -215.7, 95% CI: -406.5, -24.9; N=5; I^2=94.6%) (Figure 2). Further, in diabetic children, the central corneal thickness (µm) was higher than non-diabetic children (WMD 12.66, 95% CI: 5.47, 19.84; N=16; I^2=88.1%) (Figure 3). There were no differences in the corneal curvature (Dioptre) (WMD 0.04, 95% CI: -0.22, 0.30; N=5; I^2=0.0%) and corneal diameter (mm) (WMD 0.15, 95% CI: -0.25, 0.55; N=2; I^2=40.2%) in the two group of children (Figure 3).

Findings Related to Lens Morphology

In diabetic children, the thickness of the lens (mm) (WMD 0.25, 95% CI: 0.13, 0.36; N=4; I^2=89.1%) and lenticular density (maximum lens density; WMD 3.02, 95% CI: 2.23, 3.81; N=2; I^2=0.0 %) was higher than non-diabetic children (Figure 4). Although not statistically significant, the mean lens density (WMD 0.44, 95% CI: -0.01, 0.89; N=2; I^2=55.1%) was comparatively higher in diabetic children. There were no differences in the spherical equivalent (Dioptre) (WMD 0.03, 95% CI: -0.06, 0.12; N=3; I^2=0.0%) (Figure 4).

Findings Related to Additional Anterior Segment Morphology

The anterior chamber depth (mm) (WMD -0.17, 95% CI: -0.24, -0.09; N=5; I^2=69.4%) and pupillary diameter (mm) (WMD -0.61, 95% CI: -1.12, -0.10; N=4; I^2=75.4%) was significantly reduced in diabetic children, compared to non-diabetic children (Figure 5). There were no differences in the intra-ocular pressure (mm Hg) (WMD 0.60, 95% CI: -0.28, 1.48; N=4; I^2=63.6%), axial length (mm) (WMD -0.19, 95% CI: -0.50, 0.11; N=3; I^2=57.5%), tear film breakup time (sec) (WMD 0.42, 95% CI: -0.94, 1.79; N=2; I^2=77.5%) and Schirmer test (mm) (WMD -2.84, 95% CI: -7.74, 2.06; N=2; I^2=96.7%) between the two group of children (Figure 5).

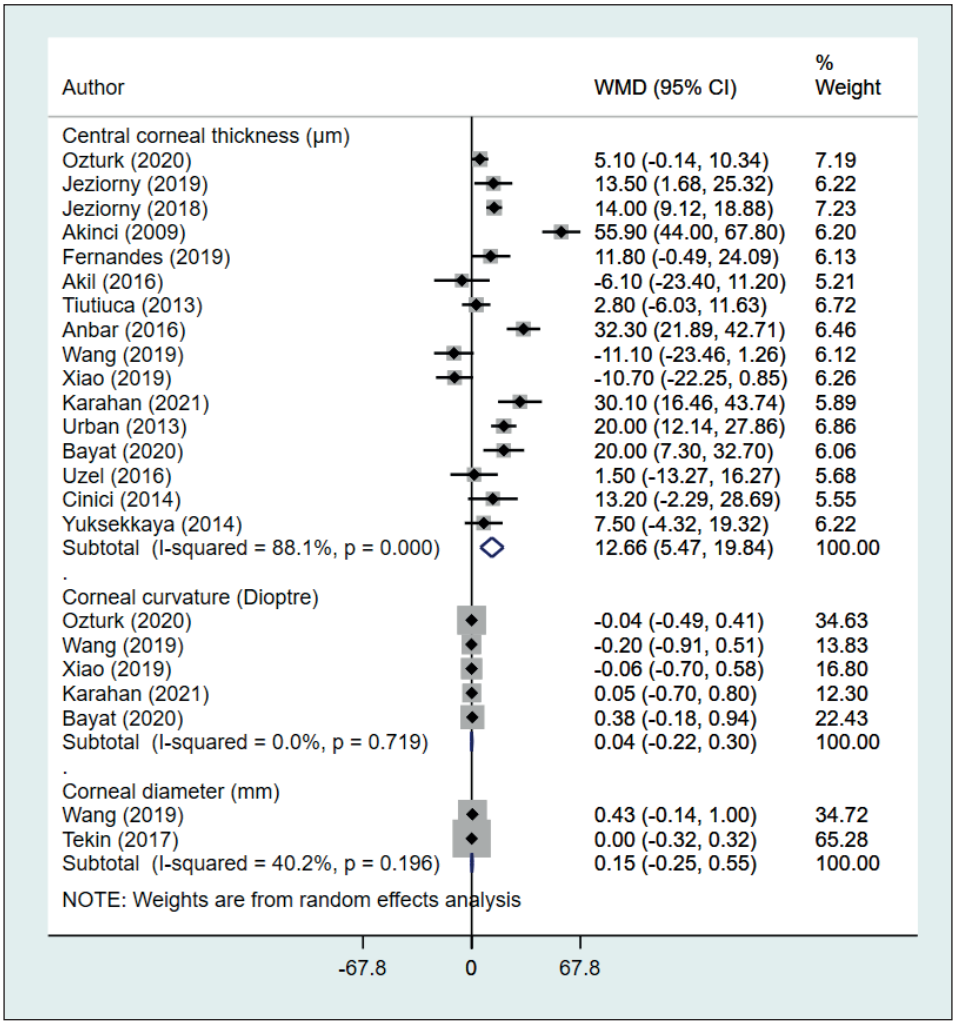

Figure 3. Comparison of central corneal thickness, corneal curvature and diameter in diabetic children, compared to normal children.

Discussion

The current meta-analysis attempted to synthesize available evidence comparing the anterior segment ocular morphology among children with and without diabetes. Through pooling of findings from 17 studies, the review found that diabetic children had lower corneal endothelial cell density, higher central corneal thickness, higher lenticular thickness and density than non-diabetic children. Anterior chamber depth and pupillary diameter were significantly reduced in diabetic children, compared to non-diabetic children. No differences in the corneal curvature, corneal diameter and spherical equivalent were noted in the two group of children. Also, there were no differences with regards to the intra-ocular pressure, axial length, tear film breakup time and Schirmer test.

The increase in central corneal thickness may be due to diabetes related changes in the corneal stroma and associated stromal oedema[48]. Studies[48,49] have suggested that there is increased accumulation of advanced glycation end products in the corneal stroma, possibly due to alternation in the collagen expression (type IV), impaired cell adhesion and increased apoptosis of keratocytes. This increased accumulation may be a precursor to the cross linking of collagen in corneal stroma which increases the corneal thickness[50]. Our review noted a decrease in the corneal endothelial cell density, and this is in concurrence with the existing literature which suggests that not only the endothelial cells decrease in number in diabetics but also the number of cells with polymegethism and pleomorphism increases[51]. Particularly in the diabetics, there is a progressive damage to the corneal endothelium due to inflammatory environment characterised

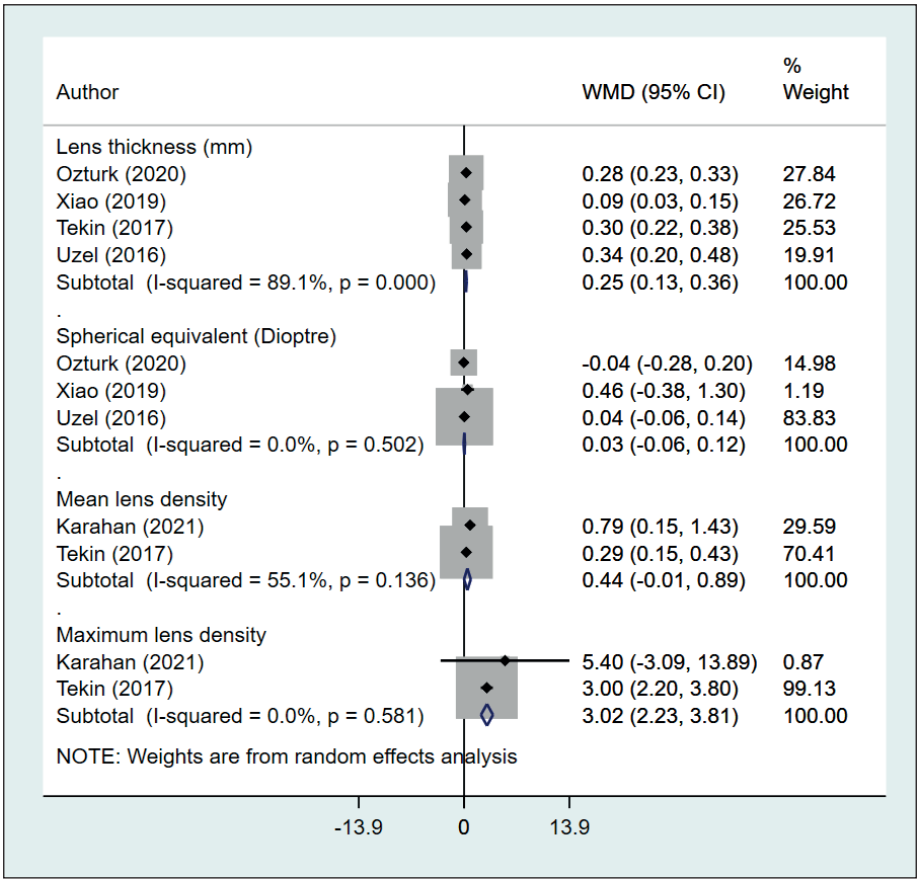

Figure 4. Comparison of lenticular morphology in diabetic children, compared to normal children.

by increased levels of vascular endothelial growth factor (VEGF), tumour-necrosis factor-alpha and interleukins such as IL-7[52]. This damage not only affects the morphology but the functioning of the endothelium as well. There is a disruption of the endothelial barrier and the recovery rate for the endothelial cells is severely impacted[52]. Further, there is an increased accumulation of glycation products and sorbitol which leads to lowering the number of corneal endothelial cells[53]. Some also suggest a role of mitochondrial dysfunction resulting in enhanced accumulation of reactive oxygen species and consequent injury to the endothelial cells[54].

In our review, we found an increase in lens thickness and density among diabetic children. These could be attributed to the osmotic changes due to changes in blood glucose levels that leads to increased hydration of the lens resulting from flow of aqueous humour into the lens[55,56]. Other possible explanation could be the impairment in the ion pump function and possibly, an increased permeability of the cell membrane[57]. We found that in diabetic children, there was a reduction in the depth of the anterior chamber. This may be due to the increased thickness of the lens. This is substantiated by studies that documented an inverse relationship of anterior chamber depth with lens thickness[40,45]. Our review also found that there was an increase in lens thickness and a consequent reduction in chamber depth. In spite of significant differences in lens morphology between diabetic and non-diabetic children, the spherical equivalent was similar in the two groups. This could be due to the compensatory reduction in the refractory index of the lens in an attempt to compensate for the increase in the thickness[55].

There were certain limitations of the review. First, all the studies were observational in design, mostly cross-sectional and therefore, the bias related to the selection of the study subjects could be present. Second, there was little variation in the geographical location where the studies were conducted with majority (n=9/17) in Turkey followed by Poland and China. Therefore, the external validity of the findings is compromised to certain extent. Third, all the studies were done

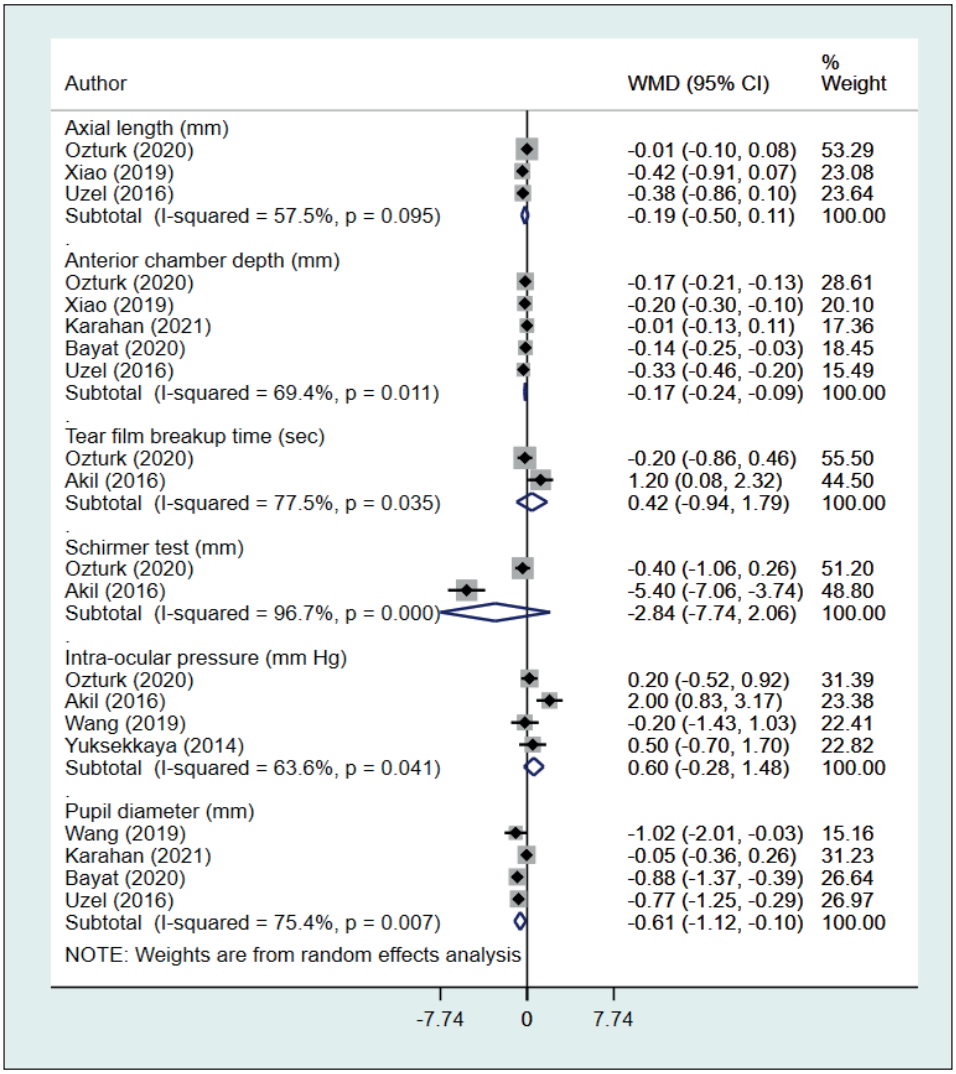

Figure 5. Comparison of anterior segment characteristics in diabetic children, compared to normal children.

among children with type 1 DM and therefore, the findings apply to this specific subset of diabetic children. It is not clear from this review whether children and adolescents with type 2 DM exhibit similar morphological changes. Fourth, the sample size of many of the included studies was under 200 and there may be a possibility that it may not have been statistically possible to show a meaningful difference in the outcomes due to lower power of the study. Future studies should aim for larger sample sizes with adequate power. Finally, it would have been worthwhile to look at the differences in the morphology in relation to the age at onset, duration of diabetes and quality of glycaemic control. However, this analysis could not be done at the included studies did not provide stratified findings based on these variables.

Conclusions

Through pooling of findings from 17 observational studies, the current review found that there were significant structural changes in cornea and lens along with reduction in anterior chamber depth and pupillary diameter. All these changes were noted in the absence of any significant refractory error. The findings are extremely crucial and suggest that these morphological changes may be indication for early and prompt management in order to prevent severe ocular damage later in life. The findings also undersco re the need for combining the routine ophthalmological examination in children and adolescents with diabetes with more advanced assessment techniques such as optical biometry and/or optical tomogra-

phy. Further, future studies should specifically examine the association of duration of diabetes and quality of glycaemic control with ophthalmological changes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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