CENTRAL CORNEAL THICKNESS AND INTRAOCULAR PRESSURE IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

DR ZULHISHAM BIN MOHMAD

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (OPHTHALMOLOGY)

UNIVERSITI SAINS MALAYSIA

2023

DISCLAIMER

I hereby certify that the work in this dissertation is my own except for quotations and summaries which have been duly acknowledged. I declare that I have no financial interest in the instruments and the computer software used in this study.

Dated: 28th May 2023

……

Dr. Zulhisham bin Mohmad P-UM0107/19

ACKNOWLEDGEMENT

In the name of Allah, the Most Merciful and Beneficent. Alhamdulillah, all praise to Allah, the Almighty, the greatest of all, on whom we ultimately, depend for sustenance and guidance. I want to thank Him for giving me the opportunity, determination, and strength to complete this manuscript.

A very special mention to my immediate supervisor, Professor Dr. Shatriah Ismail of the Ophthalmology Department and Visual Science at Universiti Sains Malaysia for her enthusiastic encouragement, patience, and continuous support throughout this arduous process. Without her support and guidance, this dissertation would not have been possible.

I would also like to express my utmost thanks and gratitude to my co-supervisor, Dr. Suhaimi Hussain for giving me the opportunity and support to conduct this study.

My warmest appreciation to all the professors, lecturers, support staff, and colleagues for supporting and assisting in this endeavour.

Finally, I must express my heartfelt gratitude to my family, my parents and in laws, Ayah, Mak dan Mama, my beloved wife, Najwa, my eldest sister Kokti and my brothers Li, Hilmi, Akmal and Fikri for their endless love, support, patience, and sacrifice. This master journey accomplishment would not have been possible without them.

Thank you.

TABLE OF CONTENTS

ABSTRAK (BAHASA MALAYSIA)

Pengenalan

Tujuan kajian ini dijalankan adalah untuk mengenal pasti min ketebalan tengah kornea dan tekanan mata untuk kanak-kanak yang menhidapi penyakit Kencing Manis Jenis 1 (T1DM). Di samping itu, kajian ini juga ingin mengenal pasti hubungan parameter tersebut dengan umur, jantina, hemoglobin A1c (HbA1c), tempoh kencing manis dan diabetik retinopati.

Kaedah kajian

Ini adalah kajian kawalan kes yang bertempat di Hospital Universiti Sains Malaysia yang dijalankan daripada Januari 2022 sehingga November 2022. Sebanyak 38 kanak-kanak yang menghidapi T1DM dan 38 kanak-kanak sihat dipelawa untuk menyertai kajian ini. Mata kanan peserta kajian ini diperiksa dengan teliti dan tekanan mata serta ketebalan tengah kornea diukur dengan alat *optical coherent tomopgraphy* (OCT).

Keputusan

Ketebalan tengah kornea dan tekanan mata didapati lebih tinggi yang signifikan di dalam kumpulan T1DM. Min ketebalan tengah kornea ialah 542.18±20.40 μm dalam kumpulan T1DM dan 529.52±26.17 μm dalam kumpulan kawalan (nilai-p <0.05). Min tekanan mata 14.74±2.05 mmHg dalam kumpulan T1DM dan 13.68±1.76 mmHg dalam kumpulan kawalan (nilai-p <0.05). Mean HbA1c ialah 10.68±2.49%. Tiada diabetik retinopati dalam kumpulan T1DM. Umur dan tempoh kencing manis mempunyai hubungan yang signifikan dengan ketebalan tengah kornea dalam kanak-

kanak yang menghidapi T1DM. Tempoh kencing manis juga mempunyai hubungan yang signifikan dengan tekanan mata. Jantina dan paras HbA1c tidak menunjukkan hubungan yang signifikan dengan ketebalan tengah kornea mata dan tekanan mata.

Kesimpulan

Kanak-kanak yang menghidapi T1DM mempunyai ketebalan tengah kornea dan tekanan mata yang lebih tinggi berbanding kanak-kanak lain. Tempoh kencing manis merupakan faktor yang mempengaruhi ketebalan tengah kornea dan tekanan mata. Umur juga merupakan faktor yang mempengaruhi ketebalan tengah kornea dalam kanak-kanak yang menghidapi T1DM.

Kata Kunci: Kanak-kanak, Kencing Manis Jenis 1, ketebalan kornea, tekanan mata

ABSTRACT

Purpose

The aim of this study is to determine the mean central corneal thickness (CCT) and mean intraocular pressure (IOP) in children with type 1 diabetes mellitus (T1DM) and to determine the relationship between CCT and IOP on the one hand and age, gender, retinopathy hemoglobin A1c (HbA1c), and duration of diabetes on the other.

Methods

This is a case–control, hospital-based study conducted at Hospital Universiti Sains Malaysia between January 2022 and November 2022. Thirty-eight children with T1DM were recruited as cases, and 38 healthy children were recruited as controls. The cases and controls then underwent ophthalmic examination, IOP measurement, and CCT measurement using optical coherence tomography (OCT) of the right eye.

Results

The CCT and IOP values were higher in the T1DM group than in the control group, and the difference was statistically significant. The mean CCT was 542.18 ± 20.40 μm in the T1DM group, and 529.52 ± 26.17 μm in the control group (*p*-value <0.05). The mean IOP was 14.74 ± 2.05 mmHg in the T1DM group, and 13.68 ± 1.76 mmHg in the control group (*p*-value <0.05). The mean HbA1c was 10.68 ± 2.49% in the T1DM group. There was no diabetic retinopathy found in T1DM group. Age and duration of diabetes mellitus (DM) were found to have a significant link with CCT in children with T1DM. The duration of DM was also found to be significantly linked to the IOP. Gender and HbA1c levels were found to have no significant relationship with either CCT or IOP.

Conclusion

Children with T1DM have significantly higher CCT and IOP than the average child. The duration of DM is a significant factor that impacts both CCT and IOP. In addition, age is another factor that affects CCT in children with T1DM.

Keywords: Children, Type 1 Diabetes Mellitus, Cornea Thickness, Intraocular Pressure

CHAPTER 1:

INTRODUCTION

1.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a chronic disease in which the pancreas is only able to produce either small amount of insulin or no insulin at all resulting in hyperglycaemia (WHO, 2019). It is estimated that about 10% of total cases of diabetes worldwide is in the form of T1DM (Paschou, 2018). The disease typically has early onset, from the age of 6 months to early adulthood (Hong et al., 2017). While some cases of T1DM first presented as diabetic ketoacidosis to emergency department, majority of the cases presented with classic symptoms of T1DM such as thirst, polyuria, polydipsia, recurrent infection, and weight loss (Hong et al., 2017).

1.1.1 Incidence of T1DM

The incidence of T1DM worldwide is estimated to be 15 per 100000 people (Mobasseri et al., 2020). In United States, it was found that the incidence of T1DM to be 21.7 per 100000 in youths aged 0-19 years (Mayer-Davis et al., 2017). In Asia, it is estimated to be about 2 to 5 cases per 100000 person-years (Hong et al., 2017). The incidence of T1DM was also found to be increasing every year around the world (Mobasseri et al., 2020).

In Malaysia, it was found that 71.8% of children with DM has T1DM. Although the age of onset varies from early childhood to young adulthood, the median age of diagnosis was 7.6 (Hong et al., 2017). In Malaysia, it was reported that the mean haemoglobin A1c (HbA1c) for children with T1DM was 10.8% with only 25% of the patients achieved targeted HbA1c of less than 7.5% (Zain et al., 2012). In comparison,

the mean HbA1c for children with T1DM in United States were lower at 8.5% but only 17-23% of the patients achieved the target HbA1c (Miller et al., 2015).

1.1.2 Pathogenesis of T1DM

The pathogenesis of T1DM revolves around the destruction of pancreatic islet β-cells leading to reduced or absent insulin production. This usually involves the innate and adaptive immunity (DiMeglio, 2018). Recognition of β-cells component as autoantigen leads to autoimmune attack. These autoantigens include insulin B chain peptide, GAD-65, IA-2, and zinc transporter 8 (ZnT8) (Giwa et al., 2020).

These autoantigens are presented by antigen presenting cells to CD4 T cells which stimulate B cells to produce more antibodies. CD4 T cells also help CD8 T cells to release cytokines which further damage the β-cells. Macrophages and other innate immune cells are also stimulated to attack the β-cells by the released cytokines (Giwa et al., 2020; Paschou, 2018).

More than 90% of patients with newly diagnosed T1DM have detected levels of antibodies targeted to these autoantigens in them (DiMeglio, 2018; Ministry of Health Malaysia, 2017). Triggers for this autoimmunity are poorly understood, but genetics, viruses such as coxsackie virus, and environmental factors such as diet have been implicated (Paschou, 2018; Giwa et al., 2020).

1.1.3 Diagnosis of T1DM

The diagnostic criteria based on Clinical Practice Guidelines in Malaysia for diabetes mellitus (DM) are as follows:

i. Classic symptoms of diabetes or hyperglycaemic crisis, with plasma glucose concentration of ≥11.0 mmol/L, or
ii. Fasting plasma glucose of ≥7.0 mmol/L, or
iii. Two-hour post-load glucose of ≥11.0 mmol/L in oral glucose tolerance test (OGTT), or
iv. HbA1c >6.5%

For T1DM, the above tests are usually supported by additional tests to indicate presence of pancreatic islet β-cells destruction such as low/undetected C-peptide levels or the presence of diabetes associated autoantibodies (Ministry of Health Malaysia, 2017).

1.1.4 Management of T1DM

Management of T1DM requires multiple approach including medical therapy with insulin, nutritional therapy, physical activity and psychosocial support (Hong et al., 2017). Monitoring control of T1DM is achieved by measuring HbA1c about 3-6 times a year. HbA1c reflects the level of glycaemia 1-3 months prior and is useful in predicting macrovascular and microvascular complications. The recommended optimal

HbA1c levels for T1DM patients below the age of 18 years is <7.5% (Ministry of Health Malaysia, 2017).

1.2 Effect of Diabetes Mellitus to the Ocular Tissues

Uncontrolled DM may cause several macrovascular and microvascular end-organ damage in the body. Persistent hyperglycaemia is thought to cause cell damage by several mechanisms such as accumulation of sorbitol via polyol pathway, accumulation of advanced glycated endproducts, activation of protein kinase C which causes inflammation, and production of radical oxygen species (Tarr et al., 2013). The eye is one of the affected organs damaged by persistent hyperglycaemia.

DM may cause thicker corneal stroma thickness. Matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) functions in synthesis and degradation of the extracellular matrix of the cornea stroma. It was reported that this balance is disrupted in patients with DM, where there were MMP-3 and MMP-10 upregulation and TIMPs-4 downregulation, increasing the synthesis of the extracellular matrix in the stroma (Zhao et al., 2019). Additionally, it is thought that the accumulation of reactive oxygen species, advanced glycated end products, and growth factors result in activation and proliferation of cornea stromal keratocytes (Zhao et al., 2019). Intraocular pressure (IOP) measurement has been found to be affected by corneal thickness. Thicker corneas tend to have higher measured IOP (Tonnu et al., 2005).

The endothelium layer of the cornea is also affected by uncontrolled DM. Its primary function is to maintain corneal deturgence. Lower endothelial cell count was

found in patients with DM compared to the normal population. This might be due to cell death caused by the mechanism described earlier (Zhao et al., 2019). Moreover, epithelial dysfunction and corneal nerve neuropathy also leads to corneal erosions and delayed wound healing (Lutty, 2013).

Hyperglycaemia is also thought to cause excess extracellular matrix synthesis in trabecular meshwork. This will sequentially cause outflow obstruction of the aqueous humor in the anterior segment in the eye and elevates the intraocular pressure (Hymowitz et al., 2016). A meta-analysis of several case-control studies and cohort studies have discovered that patients with DM have higher risk of developing primary open angle glaucoma (Zhou et al., 2014).

Poorly controlled DM may also lead to diabetic retinopathy. Diabetic retinopathy is a microvasculopathy that is characterised by serum leakage, increased vascular permeability and loss of the capillaries function in the retina (Lutty, 2013). Hyperglycaemia creates an environment which is toxic and leads to vascular endothelial cells, pericytes and neuronal cells death. There is no blood flow in acellular capillaries after pericytes death which causes hypoxia of the surrounding retina (Lutty, 2013). This upregulates vascular endothelial growth factor (VEGF) which increases vascular permeability and endothelial cell proliferation. Increased vascular permeability causes macular oedema whereas endothelial cell proliferation causes microaneurysms, intraretinal microvascular abnormalities and eventually neovascularization (Lutty, 2013). It was reported in Malaysia, retinopathy is present in about 3.2% of children with T1DM (Zain et al., 2012).

1.3 Previous studies

Fernandes et al (2019) performed a prospective cross-sectional study involving 50 children with T1DM and 50 healthy children aged 7 to 17 years in India to investigate the effect of diabetes on the corneal endothelium. In the study, they found that children with T1DM had significantly thicker (p=0.015) average central corneal thickness (CCT) than healthy children (525.16 ± 33.14 μm vs 513.44 ± 29.46 μm). They also found that the average corneal endothelial count of T1DM children was significantly lower (p<0.001) than healthy children (3039.64 ± 292.84 cells/mm^2 vs 3360.41 ± 268.04 cells/mm^2). However, they did not find any correlation between the CCT and endothelial cell count with either duration or control of diabetes.

Another study in Egypt conducted by Anbar et al (2016) was a cross sectional study to investigate corneal endothelial cell morphological changes in children with T1DM. It involved 80 children with T1DM and 80 healthy children age between 2 to 14 years. They found that the mean CCT was significantly higher in children with T1DM (right eye, 537 ± 33.41 μm vs 504.7 ± 23.99 μm; left eye, 539.91±30.49 μm vs 501.63 ± 15.77 μm). The endothelial count was also found to be significantly lower in T1DM children (right eye, 3149.84 ± 343.75 cells/mm^2 vs 3308.78 ± 99.33 cells/mm^2; left eye, 3142.13 ± 416.74 cells/mm^2 vs 3315.25 ± 100.16 cells/mm^2). They found a correlation between duration of diabetes with these changes.

A prospective cross sectional study by Akil et al (2016) in Turkey involving 42 children with T1DM and 42 healthy children age 4 to 18 years. They investigated the effect of diabetes on intraocular pressure (IOP), dry eyes (by Schirmer test and tear

break up time), central corneal thickness, total macular volume and central retinal thickness. The result was that there were statistically significant reduced Schirmer test, increased IOP and decreased retinal thickness in the T1DM group. There was no correlation between these changes with either duration of diabetes or HbA1c.

Urban et al (2013) conducted a cross sectional study in Poland involving 123 children with T1DM and 124 healthy children as control. The purpose of their study was to compare the endothelial structure of diabetic and non diabetic children and to evaluate factors that can contribute to the damage of the endothelium. They found that there is statistically significant increase in CCT in T1DM children (0.55 ± 0.03mm vs 0.53 ± 0.033mm) and statistically significant reduction in corneal endothelial count in T1DM children (2435.55 ± 443.43 cells/mm^2 vs 2970.75 ± 270.1 cells/mm^2). Both of these was found to be correlated with duration of diabetes.

1.4 Rationale of study

The study regarding corneal thickness and IOP in children with T1DM is still lacking in South East Asia. Few studies have been conducted in Europe, North Africa, Central and South Asia. As mentioned previously, children with T1DM in Malaysia achieved poorer control than those from western countries. Hence, the data obtained in this study might be different than those previously published elsewhere.

In addition to that, the outcome of this study might be useful for surveillance of children with T1DM. The result of this study could potentially be applied for IOP or glaucoma screening of children with T1DM.

Finally, the data obtained from this study can also be used as a reference value for future studies looking at the cornea and the IOP particularly for population in the paediatric age group and for those with diabetes mellitus.

1.5 References

Akil, H., Buluş, A. D., Andiran, N., & Alp, M. N. (2016). Ocular manifestations of Type 1 diabetes mellitus in pediatric population. *Indian J Ophthalmol*, **64(9)**, 654–658. https://doi.org/10.4103/0301-4738.194336

Anbar, M., Ammar, H., & Mahmoud, R. A. (2016). Corneal Endothelial Morphology in Children with Type 1 Diabetes. *J Diabetes Res*, **2016**, 1–8. doi:10.1155/2016/7319047

Fernandes, S. I., & Nagpal, S. (2019). Corneal thickness and endothelial cell density in children with type 1 diabetes mellitus. *Oman J Ophthalmol*, **12(3)**, 186–190. https://doi.org/10.4103/ojo.OJO_21_2018

DiMeglio, L. A., Evans-Molina, C., & Oram, R. A. (2019). Type 1 Diabetes. HHS Public Access. *Lancet*, **176**(**3**), 139–148. doi: 10.1016/S0140-6736(18)31320-5

Giwa, A. M., Ahmed, R., Omidian, Z., Majety, N., Karakus, K. E., Omer, S. M., Donner, T., Hamad, A. R. A. (2020). Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. *World J Diabetes*, **11**(**1**), 13–25. doi:10.4239/wjd.v11.i1.13

Hong, Y., Hassan, N., Cheah, Y. K., Jalaludin, M. Y., & Kasim, Z. M. (2017). Management of T1DM in children and adolescents in primary care. *Malays Fam Physician*, **12(2)**, 18–22.

Hymowitz, M. B., Chang, D., Feinberg, E. B., & Roy, S. (2016). Increased intraocular pressure and hyperglycemic level in diabetic patients. *PLOS ONE*, **11(3)**, e0151833. doi:10.1371/journal.pone.0151833

Lutty G. A. (2013). Effects of diabetes on the eye. *Invest Ophthalmol Vis Sci*, **54(14)**, ORSF81–ORSF87. https://doi.org/10.1167/iovs.13-12979

Mayer-Davis, E. J., Lawrence, J. M., Dabelea, D., Divers, J., Isom, S., Dolan, L., Imperatore, G., Linder, B., Marcovina, S., Petitt, D. J., Pihoker, C., Saydah, S., & Wagenknecht, L. (2017). Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. *N Engl J Med*, **376**(**15**), 1419–1429. doi:10.1056/nejmoa1610187

Miller, K. M., Foster, N. C., Beck, R. W., Bergensta, R. M., DuBose, S. N., DiMeglio, L. A., & Tamborlane, W. V. (2015). Current state of type 1 diabetes treatment in the U.S.: Updated data from the T1D exchange clinic registry. *Diabetes Care*, **38**(**6**), 971–978. doi:10.2337/dc15-0078

Ministry of Health Malaysia. (2017). *Malaysian Clinical Practice Guideline: Management Of Type 1 Diabetes Mellitus In Children & Adolescents.* Retrieved from https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/2a.pdf [Accessed on 13 September 2020]

Mobasseri, M., Shirmohammadi, M., Amiri, T., Vahed, N., Hosseini Fard, H., & Ghojazadeh, M. (2020). Prevalence and incidence of type 1 diabetes in the world: a

systematic review and meta-analysis. *Health Promot Perspect*, **10(2)**, 98–115. https://doi.org/10.34172/hpp.2020.18

Paschou, S. A., Papadopoulou-Marketou, N., Chrousos, G. P., & Kanaka-Gantenbein, C. (2018). On type 1 diabetes mellitus pathogenesis. *Endocr Connect*, **7(1)**, R38–R46. https://doi.org/10.1530/EC-17-0347

Tarr, J. M., Kaul, K., Chopra, M., Kohner, E. M., & Chibber, R. (2013). Pathophysiology of diabetic retinopathy. *ISRN Ophthalmol*, **2013**, 343560. https://doi.org/10.1155/2013/343560

Tonnu, P. A., Ho, T., Newson, T., El Sheikh, A., Sharma, K., White, E., Bunce, C., Garway-Heath, D. F. (2005). The influence of central corneal thickness and age on intraocular pressure measured by pneumotonometry, non-contact tonometry, the Tono-Pen XL, and Goldmann applanation tonometry. *Br J Ophthalmol*, **89(7)**, 851–854. doi:10.1136/bjo.2004.056622

Urban, B., Raczyńska, D., Bakunowicz-Łazarczyk, A., Raczyńska, K., & Krętowska, M. (2013). Evaluation of corneal endothelium in children and adolescents with type 1 diabetes mellitus. *Mediators Inflamm*, **2013**, 913754. https://doi.org/10.1155/2013/913754

World Health Organization. (2019). *Diabetes*. Retrieved from https://www.who.int/health-topics/diabetes [Accessed on 25 December 2020]

Zain, F. M., Hong, J. Y. H., Wu, L. L., Harun, F., Rasat, R., Jalaludin, M. Y., Bujang, M. A., & Supramaniam, P. (2012). *2nd Report of Diabetes in Children and Adolescents Registry (DiCARE) 2006 - 2008*. Retrieved from https://www.crc.gov.my/wp-content/uploads/2014/08/Annual_Report_of_The_Diabetes_In_Children_And_Adolescents_Registry_2006_2008.pdf

Zhao, H., He, Y., Ren, Y. R., & Chen, B. H. (2019). Corneal alteration and pathogenesis in diabetes mellitus. *Int J Ophthalmol*, **12(12)**, 1939–1950. https://doi.org/10.18240/ijo.2019.12.17

Zhou, M., Wang, W., Huang, W., & Zhang, X. (2014). Diabetes mellitus as a risk factor for open-angle glaucoma: A systematic review and meta-analysis. *PLoS ONE*, **9(8)**. doi:10.1371/journal.pone.0102972

CHAPTER 2:

OBJECTIVES

2.1 General Objectives

To evaluate the central corneal thickness and intraocular pressure in children with T1DM.

2.2 Specific Objectives

1. To compare the mean central corneal thickness between children with T1DM and healthy non diabetic children.

2. To compare the mean intraocular pressure between children with T1DM and healthy non diabetic children.

3. To determine the association of the central corneal thickness with age, gender, HbA1c, duration of diabetes and presence of retinopathy in children with T1DM.

4. To determine the association of the intraocular pressure with age, gender, HbA1c, duration of diabetes and presence of retinopathy in children with T1DM.

CHAPTER 3:

MANUSCRIPT