EVALUATION OF THE RETINAL VASCULAR CALIBRES AND ITS ASSOCIATED FACTORS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

DR MUHD SYAFI BIN ABD BARI

THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF MEDICINE (OPHTHALMOLOGY)

UNIVERSITI SAINS MALAYSIA

2021

DISCLAIMER

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

Date: **11TH MAY 2021**

_____

DR MUHD SYAFI BIN ABD BARI

ACKNOWLEDGEMENT

All praises to Allah S.W.T the Most Merciful and the Most Beneficent. I am grateful to Allah The Almighty, for giving me strength, patience and continuous health throughout my research journey.

A very special gratitude goes out to my main supervisor, beloved Professor Dr Hajjah Shatriah Bt Ismail for her active guidance and encouragement to accomplish this journey. Thank you for mentoring and being a dedicated supervisor to me. Her absolute conscientiousness added priceless experience in my learning process.

I am ineffably indebted to my co-supervisor, Dr Evelyn Tai Li Min and Dr Suhaimi Bin Hussain for their nonstop and continuous supervisions, supports and inspirations. Thank you for being very kind, patience and understanding.

I wish to express my sincere thanks to all Ophthalmology lecturers and staff for assisting me during this project.

Thank you to my parents, Hj Abd Bari bin Ahmad and my mother Hajjah Salmi Bt Abas, both my parent-in-law, Wawa, my wife, Dr Dhamirah Nazihah, and children (Ahmad Ayyash, Haura' and Ahmad Wa'iz) for the support and encouragement throughout this journey. This accomplishment would not have been possible without them. May Allah bless them all.

Thank you to my fellow study groupmates; Dr Ikmal, Dr Hudzaifah, Dr Khairil Ridzuan, Dr Mas Edi and Dr Khairul Anwar for the beautiful memories of sharing knowledge and valuable experience together.

Last but not least, I am thankful to Ministry of Higher Education and International Islamic University of Malaysia for providing me the scholarship to fulfil my career goals and for supporting this study under one of the grants.

Any omission in this brief acknowledgement does not mean lack of gratitude.

TABLE OF CONTENT

ABSTRAK

Latar belakang: Kadar glisemik yang tidak terkawal pada pesakit kencing manis jenis 1 berkait rapat dengan peningkatan risiko komplikasi mikrovaskular. Kajian kami bertujuan untuk menentukan purata saiz kaliber arteri dan vena antara kadar glisemik yang terkawal dan tidak terkawal pada lawatan awal, pertengahan dan terakhir. Kami juga melihat faktor-faktor yang boleh mempengaruhi saiz kaliber salur darah retina pada kanak-kanak yang mempunyai kencing manis jenis 1.

Kaedah: Kajian ini berasaskan hospital prospektif keratan rentas yang melibatkan kanak-kanak kencing manis jenis 1. Para peserta direkrut dari Klinik Oftalmologi dan Kanak-Kanak Hospital Universiti Sains Malaysia. Gambar fundus mata kanan diambil pada setiap lawatan awal, pertengahan dan terakhir dan dianalisa oleh Singapore 1 Vessels Analysis (SIVA). Kadar HbA1c pada setiap lawatan juga didokumentasikan pada setiap lawatan.

Ukuran Hasil Utama: Purata saiz kaliber arteri (CRAE) dan kaliber vena (CRVE) di kalangan kawalan glisemik yang terkawal dan tidak terkawal ditentukan pada setiap lawatan dan faktor-faktor yang berkaitan dengan saiz kaliber salur darah retina dianalisa.

Hasil: Purata usia peserta adalah 12.5 (2.24) tahun. Majoriti peserta adalah berbangsa Melayu dan kebanyakannya mempunyai kadar glisemik yang tidak terkawal. Purata kaliber CRAE dan CRVE tidak berbeza secara signifikan bagi kedua-dua kumpulan pada setiap lawatan. Walau bagaimanapun, purata CRVE lebih lebar secara signifikan ($p=0.037$) di kalangan peserta yang mempunyai kadar glisemik tidak terkawal sepanjang

tempoh rawatan susulan. Umur, jangka masa kencing manis, tekanan darah, BMI dan HbA1c tidak mempunyai kaitan dengan saiz kaliber salur darah retina.

Kesimpulan: CRVE yang lebih lebar mempunyai kaitan dengan kadar glisemik yang tidak terkawal. Ini boleh menjadi salah satu petunjuk awal dalam mengesan perkembangan komplikasi retinopati. Dalam jangka masa kajian susulan yang pendek ini, tidak ada faktor yang signifikan berkaitan usia, tempoh, tekanan darah, BMI dan kawalan glisemik dengan saiz kaliber vaskular retina.

Kata kunci: Kencing manis jenis 1, kaliber salur darah, kawalan glisemik, CRAE, CRVE

ABSTRACT

Background: Poor glycaemic control in patients with type 1 diabetes mellitus (Type 1 DM) is closely associated with an increased risk of microvascular complications. Our study aims to determine the mean retinal arteriolar and venular calibres between the good and poor glycaemic control at baseline visit, mid visit and last visit. We also look into the co-factors associated with the retinal vascular calibres in children with type 1 DM.

Methods: A cross-sectional prospective hospital-based study involving children with Type 1 DM. The participants were recruited from Ophthalmology and Paediatric Clinics of Universiti Sains Malaysia Hospital. Fundus photo of right eye were taken at baseline, mid and final visit and analysed by Singapore 1 Vessels Analysis (SIVA). HbA1c at each visit were documented.

Main Outcome Measure: Mean central arteriolar equivalent (CRAE) and venular equivalent (CRVE) in good and poor glycaemic control were determined at each visit and its associated factors were analysed.

Results: The mean presenting age were 12.5 (2.24) years old. Majority of the participants were Malay race and mostly had poor glycaemic control. The mean CRAE and CRVE were not significantly differ for both group at each visit. However, the mean CRVE were significantly wider (p=0.037) in poor glycaemic control along the duration of follow up. Age, duration of DM, blood pressure, BMI and HbA1c are not associated with vascular calibres.

Conclusion: A wider CRVE is associated with poorly glycaemic control DM. It can be one of earlier indicator in detecting the progression to diabetic retinopathy. In this closer and shorter duration of follow up study, no significant associated factors between age, duration, blood pressure, BMI and glycaemic control with retinal vascular calibres.

Keyword: Type 1 DM, vascular calibres, glycaemic control, CRAE, CRVE

CHAPTER 1 | INTRODUCTION

1.1 Incidence and Prevalence of Type 1 DM

The International Diabetic Federation estimated the prevalent cases of type 1 diabetes mellitus worldwide were 1,110100 with an incident of 128900 cases per year (IDF, 2019). The average increase is about 3-4% per year over past decades has been highlighted and a significant increment of cases in previously low incidence countries has been reported (Tuomilehto & Jaakko, 2013). The incidence of type 1 diabetes mellitus was reported the lowest in East and South-East Asian region. However, Mobasseri *et al* in their systemic review and meta-analysis study found that the incidence of type 1 diabetes in Asia region was 15 per 100 000 population and the prevalence of type 1 diabetes was 6.9 per 10 000 people (Mobasseri *et al.,* 2020). Meanwhile, a few literature addressed an increase number of type 1 diabetes in their population such as in studies by Desai *et al.* in India, Weng *et al.* in China and particularly Southeast Asia (Weng *et al.*, 2018; Desai & Deshmukh, 2019; Pulungan, Fadiana & Annisa, 2021).

In Malaysia, type 1 DM was estimated to account for 69.2% of children and adolescents with diabetes (Fauziah *et al.,* 2008). Diabetes in Children and Adolescents Registry (DiCARE) was launched nationwide in August 2006 to provide a uniform data collection system of diabetes mellitus among three main ethnics group in Malaysia. This online registry aiming for participant with diabetes mellitus who aged less than 20 years old from hospitals in Malaysia. The outcome result of this study revealed incidence of diabetes mellitus among the three major ethnic groups in Malaysia were constituted of Malays 45.4%, Chinese 32.5% and Indians 19.2% (Fuziah *et al.*, 2008).

Malaysian national data from National Health Morbidity Survey showed that Malays constitute 65.1%, Chinese 26.0% and Indians 7.7% of the population. It also showed there is presence of positive family history of diabetes in 22 patients (13.3%) of Type 1 Diabetes Mellitus (Type 1 DM) patients and 27 (64.3%) of Type 2 Diabetes Mellitus patients (Fuziah *et al.*, 2008).

Total of 166 patients were included in this registry and the clinical presentation was identified in 162 patients at diagnosis. These presentations included hyperosmolar symptoms (62.8%), diabetic ketoacidosis (57.1%) and weight loss (50%). The biochemical characteristics at the time of diagnosis included random blood sugar (RBS) more than 11.1 mmol/L (89.1%), ketonuria (68.6%) and bicarbonate (HCO3) less than 15mmol/L (39.4%). Only 2.9% of these patients had insulin auto-antibodies measured and 12.4% had C-peptide or insulin level tested. This may reflect the unavailability of these tests in most centres.

1.2 Pathogenesis of Type 1 DM

Type 1 diabetes mellitus is a serious chronic disease that results from a lack of endogenous insulin secretion by the pancreatic β- cells. Although β- cell-targeted autoimmune processes and β- cell dysfunction is known to occur in type 1 DM, the precise aetiology and pathological mechanisms are still unclear. Most of the studies believes that type 1 DM is primarily caused by pancreatic islet β-cell destruction leading to severe insulin deficiency (Diabetes, 2009; Gallen, 2013; Kazi & Blonde, 2001). Type 1 diabetes mellitus is a heterogeneous disease with multiple different features. Two major pathogenesis of this disease were either insulin autoantibodies or glutamic acid

decarboxylase autoantibodies detection (Ilonen, Lempainen & Veijola, 2019). However, other studies believe that there is role of genetic association such as HLA DQ8, HLADQ2, HLA DQA1 AND HLA DQB1in its pathogenesis (Eerligh *et al.*, 2011; Van Lummel *et al.*, 2012; Pathiraja *et al.*, 2015)

Diagnosis of diabetes can be made by present of its classic symptoms (eg: polyuria, polydipsia and polyphagia) and diagnostic test as recommended by World Health Organization 2019. Patient with fasting venous plasma values of ≥ 7.0 mmol/L (126 mg/dl), 2-hour post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), HbA1c ≥ 6.5% (48 mmol/mol); or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes. However, if these values are elevated in asymptomatic patient, a repeated testing is recommended to confirm the diagnosis (WHO, 2019).

1.3 Glycaemic Control of Type 1 DM

In diabetic patient, the glycaemic level needs to be monitored. Glycated haemoglobin level (HbA1c) has been used as a biomarker to monitor the level of glucose among diabetic patient and used as a standard of care for testing and monitoring diabetes (Lyons et al., 2012)**.** HbA1c reflects the levels of glycaemia over the preceding 4 to 12 weeks by measuring the predicted half-life of red blood cells (Philips & Patrick J, 2012). It provides a reliable measurement of chronic glycaemia and correlates with the risk of long-term diabetes complications, thus it is considered the test of choice for monitoring and chronic management of diabetes (Sherwani et al., 2016). However, the cut-point of HbA1c from the diagnostic point of view is varies among diabetic association and countries.

In Malaysia, it is recommended that every diabetic patient should have a minimum of one measurement of HbA1c per year, ideally 3 to 6 measurements per year. This biomarker measurement is depending on age and degree of glycaemic control of individual patient. The recommended HbA1c target for all patients younger than 18 years is less than 7.5% (58 mmol/mol)(Ministry of Health Malaysia, 2015).

1.4 Diabetes Mellitus and Complications

Diabetes complication can be divided into microangiopathy such as retinopathy, nephropathy or neuropathy and macroangiopathy such as stroke, coronary artery disease and peripheral artery disease. In diabetic microangiopathy, it is due to the thickening of the capillary basement membrane and extracellular matrix protein synthesis, induced by microvasculature changes in diabetes. These pathognomonic features affect the arterioles of the glomeruli, retina, myocardium, skin and muscles (Roy *et al*, 2010; Chawla *et al*., 2016). These changes in conjunction with advanced glycation end products, oxidative stress, low grade inflammation, and neovascularization of vasa vasorum can lead to macrovascular complications.

The long term macrovascular, microvascular and neurologic complications had cause major morbidity and mortality in patients with Type 1 DM. An intensive therapy can effectively delays the onset and slows the progression of complication such as diabetic retinopathy, nephropathy and neuropathy in patients with Type 1 DM by a range of 39% to 76% (Barr, 2001). In Diabetes Control and Complications Trial (DCCT) and its follow up study by Epidemiology of Diabetes Interventions and Complications (EDIC), they provide a clear evidence in adults and adolescents with a good glycaemic control and

intensive treatment, it can be delayed and reduced the microvascular complications in diabetic patient.

1.5 Diabetic Retinopathy

Diabetic retinopathy (DR) is a potentially blinding complication of diabetes mellitus. It can be caused by diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR) such as vitreous haemorrhage, tractional retinal detachment, and neovascular glaucoma (Nentwich *et al.*, 2015). Diabetic retinopathy can lead to retinal ischaemia, increase retinal permeability, retinal neovascularization and macular oedema (Shin *et al.*, 2014; Wang *et al.*, 2018). The risk of developing diabetic retinopathy in patients with diabetes mellitus is related to severities of hyperglycaemia and presence of hypertension. In type 2 diabetes mellitus patients, retinopathy was reported to be related with the incidence of myocardial infarction and death due to cardiovascular disease (Klein *et al*., 2004; Van Hecke *et al*., 2005). Other studies also reported an increasing incidence of clinical stroke was associated with retinal microvascular abnormalities and generalized arteriolar narrowing (Mitchell *et al.*, 2005; Yatsuya *et al.*, 2010). The postulated theory behind this is that the retinal microvasculature shares similar embryologic and anatomic characteristics of cerebral and cardiovascular circulation.

Diabetic retinopathy is classified according to the presence or absence of abnormal new vessels as: Non-Proliferative Retinopathy or Proliferative Retinopathy with a different prognosis for vision for each. Non-proliferative diabetic retinopathy (NPDR) as in the International American Academy of Ophthalmology Classification is graded as mild, moderate and severe. Mild NPDR is characterized by the presence of a few microaneurysms. Moderate NPDR which is characterized by the presence of

microaneurysms, intraretinal haemorrhages or venous beading that do not reach the severity of the standard photographs.

Severe NPDR, is the key level to identify. Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that eyes in patients with Type 2 Diabetes Mellitus that reach the grade of severe NPDR have a 50% chance of developing high risk characteristics if laser treatment is not instituted. The diagnosis of severe NPDR is based on the 4:2:1 rule of the ETDRS. Severe NPDR is diagnosed if haemorrhages are present in all four quadrants, two quadrants or more have venous beading and one or more quadrants has intraretinal microvascular abnormalities.

In proliferative diabetic retinopathy (PDR), it is characterised by neovascularization of the disc, or elsewhere in the retina, neovascularization of the iris or angle, vitreous haemorrhage or presence of tractional retinal detachment. The macula should be examined for presence of macular oedema. If it is present then it can be further classified as mild, moderate and severe depending on the distance of the exudates and thickening from the centre of the fovea.

A patient with type 1 DM should have an initial dilated and comprehensive eye exam within five years of the onset of diabetes. Patient with either type 1 or type 2 DM should have subsequent eye exams annually, performed by an ophthalmologist or optometrist knowledgeable and experienced in diagnosing retinopathy (Fong *et al.*, 2004; Solomon *et al.*, 2017).

1.6 Retinal Vessels Anatomy

The ophthalmic artery enters the orbit on the inferolateral side of the optic nerve and gives off the central retinal artery and posterior ciliary arteries near the orbital apex. The retina is supplied by the central retinal artery and the short posterior ciliary arteries. The central retinal artery travels in or beside the optic nerve as it pierces the sclera then branches to supply the layers of the inner retina. The central artery of the retina emerges from the disc and divides into upper and lower branches. Each branch is further divides into nasal and temporal branches with no anastomoses (Snell *et al*., 2013; Kanski *et al.*, 2015).

The arteries are accompanied by veins. The arteries are brighter red in colour, smaller calibre than veins and have a brighter longitudinal colour due to light reflection from the wall. The veins are normally pulsating whilst arteries do not. Retinal venules and veins coalesce into the central retinal vein. Venous are drained out from the eye via the vortex veins and the central retinal vein, which merge with the superior and inferior ophthalmic veins. It then drains into the cavernous sinus, the pterygoid venous plexus and the facial vein.

1.7 Analysis of Retinal Vascular Calibre

The retinal microvasculature is the only part of the human circulation system available for a direct and non-invasive observations. The association between systemic and retinal hemodynamic changes with diabetes is well documented. Retinal vasculature variations, such as vessel calibre, branching angle, tortuosity and fractal dimension have been shown to be potential markers of diabetic complications (Nguyen et al, 2007; Ikram et al, 2006) including retinopathy and nephropathy (Klein, 2004; Wong *et al.*, 2004; Alibrahim *et al.*, 2006; Cheung *et al.*, 2008; Sasongko *et al.*, 2012; Ikram *et al.*, 2013; Lombardo *et al.*, 2013).

Extensive research by the Singapore Eye Research Institute (SERI) has established that assessment of retinal vascular changes may provide important predictive and prognostic information regarding risk of stroke, coronary heart disease, hypertension, diabetes and other conditions. National University of Singapore computer scientists in collaboration with SERI developed the Singapore "I" Vessel Assessment (SIVA) software to extract retinal vascular structure and describe the retinal vessels' characteristics.

SIVA can automatically extract the retinal vascular parameters information including retinal vascular calibre, tortuosity, branching angle, fractal dimension and junction exponent deviation from retinal fundus photograph. Other automation of SIVA includes retinal vasculature tracing, vessel type classification (venule or arteriole), optic disc detection and position the measured grid following the Atherosclerosis Risk in Communities Study protocol.

For measuring retinal microvascular geometric properties, Sasongko *et. al* and Cheung *et. al* had described in detail regarding the technique in their studies (Sasongko, 2010; Cheung *et al.*, 2015). Right eye retinal photographs of each patient were analysed using a semiautomated computer-assisted image program SIVA. Retinal photographs that were centred on the optic disc were viewed. For each retinal photograph, a trained grader, masked to participants' identities, applied the program to measure retinal microvascular geometric parameters within a concentric zone between the optic disc margin and two optic disc diameters away from the optic disc margin.

The grader allowed the software to detect the centre of the optic disc and divided the region into three subzones (A, B, and C) surrounding the optic disc, each zone corresponding to 0.5, 1.0, and 2.0 optic disc diameters away from the optic disc margin, respectively as shown in Figure 1. Once the optic disc and the three concentric subzones were considered appropriately located, the grader executed the program to trace all vessels.

This software has an ability of 70–90% to appropriately detect arterioles and venules. However, the grader checked each graded image to see if all arterioles and venules were correctly identified, based on information of parent vessels, crossing between arterioles and venules and the colour of the vessels. Corrections were made, if necessary. Graders were trained and tested for his or her ability in identifying arterioles and venules by a senior grader.

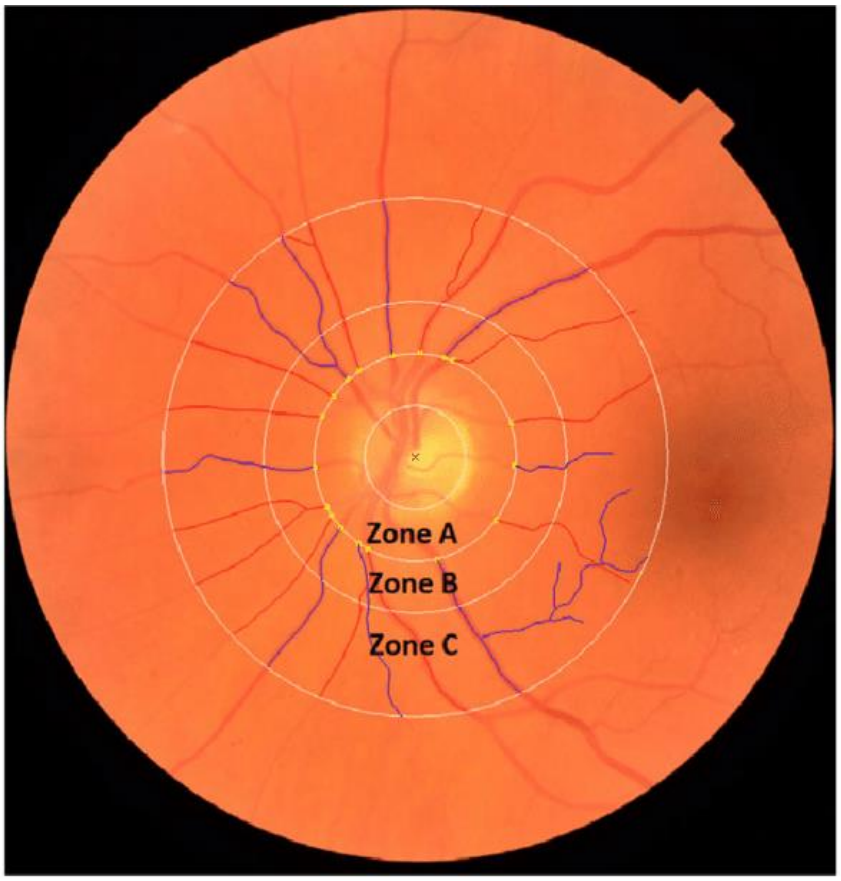

Figure 1: Fundus photo centred on the optic disc and divided into three subzones (A, B and C) by SIVA software.

1.8 References

Fuziah, M.Z., Hong, J.Y., Zanariah, H., Harun, F., Chan, S.P., Rokiah, P., Wu, L.L., Rahmah, R., Jamaiyah, H., Geeta, A. and Chen, W.S., 2008. A national database on children and adolescent with diabetes (e-DiCARE): results from April 2006 to June 2007. *Med J Malaysia*, *63* (Suppl C), pp.37-40.

Hong, Y.H.J., Hassan, N., Cheah, Y.K. and Jalaludin, M.Y., 2017. Management of T1DM in children and adolescents in primary care. *Malaysian Family Physician*, *12*(2), pp.18-22.

Mobasseri, M., Shirmohammadi, M., Amiri, T., Vahed, N., Fard, H.H. and Ghojazadeh, M., 2020. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. *Health promotion perspectives*, *10*(2), p.98.

Phillips, P.J., 2012. HbA1c and monitoring glycaemia. Australian family physician, 41(1/2), pp.37-40.Pulungan, A.B., Fadiana, G. and Annisa, D., 2021. Type 1 diabetes mellitus in children: experience in Indonesia. *Clinical Pediatric Endocrinology*, *30*(1), pp.11-18.

Tuomilehto, J., 2013. The emerging global epidemic of type 1 diabetes. Current diabetes reports, 13(6), pp.795-804.

Weng, J., Zhou, Z., Guo, L., Zhu, D., Ji, L., Luo, X., Mu, Y. and Jia, W., 2018. Incidence of type 1 diabetes in China, 2010-13: population based study. *Bmj*, *360*.

Barr, C.C., 2001. Retinopathy and Nephropathy in Patients With Type 1 Diabetes Four Years After a Trial of Intensive Insulin Therapy, by The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. N. Engl. J. Med 342: 381-9, 2000. Survey of ophthalmology, 45(5), pp.459-460.

Cheung, C.Y., Ikram, M.K., Klein, R. and Wong, T.Y., 2015. The clinical implications of recent studies on the structure and function of the retinal microvasculature in diabetes. Diabetologia, 58(5), pp.871-885.

Fuller, J.H., Stevens, L.K. and Wang, S.L., 2001. Risk factors for cardiovascular mortality and morbidity: The WHO multinational study of vascular disease in diabetes. Diabetologia, 44(2), pp.S54-S64.

Desai, S. & Deshmukh, A. (2019) Mapping of Type 1 Diabetes Mellitus. Current Diabetes Reviews, 16(5), 438–441.

DeFronzo, R.A., 2009. From the triumvirate to the „ominous octet": a new paradigm for the treatment of type 2 diabetes mellitus. Clinical Diabetology, 10(3), pp.101-128.

Eerligh, P., Van Lummel, M., Zaldumbide, A., Moustakas, A.K., Duinkerken, G., Bondinas, G., Koeleman, B.P.C., Papadopoulos, G.K. and Roep, B.O., 2011. Functional

consequences of HLA-DQ8 homozygosity versus heterozygosity for islet autoimmunity in type 1 diabetes. Genes & Immunity, 12(6), pp.415-427.

Lyons, T.J. and Basu, A., 2012. Biomarkers in diabetes: hemoglobin A1c, vascular and tissue markers. Translational Research, 159(4), pp.303-312.

Sherwani, S.I., Khan, H.A., Ekhzaimy, A., Masood, A. and Sakharkar, M.K., 2016. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. Biomarker insights, 11, pp.BMI-S38440.

Chawla, A., Chawla, R. and Jaggi, S., 2016. Microvasular and macrovascular complications in diabetes mellitus: distinct or continuum?. Indian journal of endocrinology and metabolism, 20(4), p.546.

Roy, S., Ha, J., Trudeau, K. and Beglova, E., 2010. Vascular basement membrane thickening in diabetic retinopathy. Current eye research, 35(12), pp.1045-1056.

Nentwich, M.M. and Ulbig, M.W., 2015. Diabetic retinopathy-ocular complications of diabetes mellitus. World journal of diabetes, 6(3), p.489.

Fong, D.S., Aiello, L., Gardner, T.W., King, G.L., Blankenship, G., Cavallerano, J.D., Ferris, F.L. and Klein, R., 2004. Retinopathy in diabetes. Diabetes care, 27(suppl 1), pp.s84-s87.

Wang, W. and Lo, A.C., 2018. Diabetic retinopathy: pathophysiology and treatments. International journal of molecular sciences, 19(6), p.1816.

Shin, E.S., Sorenson, C.M. and Sheibani, N., 2014. Diabetes and retinal vascular dysfunction. Journal of ophthalmic & vision research, 9(3), p.362.

Xu, X.H., Sun, B., Zhong, S., Wei, D.D., Hong, Z. and Dong, A.Q., 2020. Diabetic retinopathy predicts cardiovascular mortality in diabetes: a meta-analysis. BMC Cardiovascular Disorders, 20(1), pp.1-8.

Targher, G., Bertolini, L., Zenari, L., Lippi, G., Pichiri, I., Zoppini, G., Muggeo, M. and Arcaro, G., 2008. Diabetic retinopathy is associated with an increased incidence of cardiovascular events in Type 2 diabetic patients. Diabetic Medicine, 25(1), pp.45-50.

Cheung, N., Wang, J.J., Klein, R., Couper, D.J., Sharrett, A.R. and Wong, T.Y., 2007. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes care, 30(7), pp.1742-1746.

Snell, R.S. and Lemp, M.A., 2013. Clinical anatomy of the eye. John Wiley & Sons.

Kanski, J.J. and Bowling, B., 2015. Kanski's clinical ophthalmology e-book: a systematic approach. Elsevier Health Sciences.

Ikram, M.K., Cheung, C.Y., Lorenzi, M., Klein, R., Jones, T.L. and Wong, T.Y., 2013. Retinal vascular caliber as a biomarker for diabetes microvascular complications. Diabetes care, 36(3), pp.750-759.

Nguyen, T.T., Wang, J.J., Islam, F.A., Mitchell, P., Tapp, R.J., Zimmet, P.Z., Simpson, R., Shaw, J. and Wong, T.Y., 2008. Retinal arteriolar narrowing predicts incidence of diabetes: the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. Diabetes, 57(3), pp.536-539.

Klein, R., Klein, B.E., Moss, S.E., Wong, T.Y., Hubbard, L., Cruickshanks, K.J. and Palta, M., 2004. The relation of retinal vessel caliber to the incidence and progressionof diabetic retinopathy: Xix: The wisconsin epidemiologic study of diabetic retinopathy. Archives of ophthalmology, 122(1), pp.76-83.

Wong, T.Y., Shankar, A., Klein, R. and Klein, B.E., 2004. Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. Diabetes, 53(1), pp.179-184.

Alibrahim, E., Donaghue, K.C., Rogers, S., Hing, S., Jenkins, A.J., Chan, A. and Wong, T.Y., 2006. Retinal vascular caliber and risk of retinopathy in young patients with type 1 diabetes. Ophthalmology, 113(9), pp.1499-1503.Asongko, M. U. B. A. Y. U. S. (2010) Alterations in Retinal Microvascular Geometry in Young Type 1 Diabetes., 33(6).

Cheung, N., Rogers, S.L., Donaghue, K.C., Jenkins, A.J., Tikellis, G. and Wong, T.Y., 2008. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. Diabetes care, 31(9), pp.1842-1846.

Sasongko, M.B., Wang, J.J., Donaghue, K.C., Cheung, N., Benitez-Aguirre, P., Jenkins, A., Hsu, W., Lee, M.L. and Wong, T.Y., 2010. Alterations in retinal microvascular geometry in young type 1 diabetes. Diabetes care, 33(6), pp.1331-1336.

Lombardo, M., Parravano, M., Serrao, S., Ducoli, P., Stirpe, M. and Lombardo, G., 2013. Analysis of retinal capillaries in patients with type 1 diabetes and nonproliferative diabetic retinopathy using adaptive optics imaging. Retina, 33(8), pp.1630-1639.

Sasongko, M.B., Wong, T.Y., Donaghue, K.C., Cheung, N., Jenkins, A.J., Benitez-Aguirre, P. and Wang, J.J., 2012. Retinal arteriolar tortuosity is associated with retinopathy and early kidney dysfunction in type 1 diabetes. American journal of ophthalmology, 153(1), pp.176-183.

Grafham, G.K., 2020. The Capacity for Skeletal Muscle to Repair after Exercise-Induced Muscle Damage in Young Adults with Type 1 Diabetes Mellitus (Doctoral dissertation).

Nekoua, M.P., Dechaumes, A., Sane, F., Alidjinou, E.K., Moutairou, K., Yessoufou, A. and Hober, D., 2020. Enteroviral Pathogenesis of Type 1 Diabetes: The Role of Natural Killer Cells. Microorganisms, 8(7), p.989.

Kazi, A.A. and Blonde, L., 2001. Classification of diabetes mellitus. Clinics in laboratory medicine, 21(1), pp.1-13.

Van Lummel, M., van Veelen, P.A., Zaldumbide, A., de Ru, A., Janssen, G.M., Moustakas, A.K., Papadopoulos, G.K., Drijfhout, J.W., Roep, B.O. and Koning, F., 2012. Type 1 diabetes-associated HLA-DQ8 transdimer accommodates a unique peptide repertoire. Journal of Biological Chemistry, 287(12), pp.9514-9524.

Mitchell, P., Wang, J.J., Wong, T.Y., Smith, W., Klein, R. and Leeder, S.R., 2005. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology, 65(7), pp.1005-1009.

Yatsuya, H., Folsom, A.R., Wong, T.Y., Klein, R., Klein, B.E. and Sharrett, A.R., 2010. Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. Stroke, 41(7), pp.1349-1355.

Pathiraja, V., Kuehlich, J.P., Campbell, P.D., Krishnamurthy, B., Loudovaris, T., Coates, P.T.H., Brodnicki, T.C., O'Connell, P.J., Kedzierska, K., Rodda, C. and Bergman, P., 2015. Proinsulin-specific, HLA-DQ8, and HLA-DQ8-transdimer–restricted CD4+ T cells infiltrate islets in type 1 diabetes. Diabetes, 64(1), pp.172-182.

Solomon, S.D., Chew, E., Duh, E.J., Sobrin, L., Sun, J.K., VanderBeek, B.L., Wykoff, C.C. and Gardner, T.W., 2017. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes care, 40(3), pp.412-418.

CHAPTER 2 | OBJECTIVES

2.1 General objective

To evaluate the mean retinal vascular calibres and its associated factors in children with Type 1 DM.

2.2 Specific objectives

1. To compare the mean retinal arteriolar calibre between good and poor glycaemic control at study baseline, mid visit and final visit in children with Type 1 DM.
2. To compare the mean retinal venular calibre between good and poor glycaemic control at study baseline, mid visit and final visit in children with Type 1 DM.
3. To identify the factors affecting retinal vessels calibre in children with Type 1 DM.

2.3 Research hypothesis

1. There is difference in mean retinal arteriolar calibre between good and poor glycaemic control in children with Type 1 DM at study baseline, mid visit and final visit.
2. There is difference in mean retinal venular calibre between good and poor glycaemic control in children with Type 1 DM at study baseline, mid visit and final visit.
3. There are several factors significantly affecting retinal vessels calibre in children with Type 1 DM.

CHAPTER 3 | MANUSCRIPT

3.1 Title

Evaluation of The Retinal Vascular Calibres and Its Associated Factors in Children with Type 1 Diabetes Mellitus

Authors

Muhd Syafi Abd Bari MBBCh [1,3,4], Evelyn Tai Li Min MMed[1,3], Suhaimi Hussain MMed[2,3], Shatriah Ismail MMed[1,3]

Affiliation

[1] Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[2] Department of Paediatric, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Malaysia

[3] Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[4] Department of Ophthalmology, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

Corresponding author

Professor Dr Shatriah Ismail
Department of Ophthalmology and Visual Science, School of Medical Sciences,
Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Email: shatriah@usm.my

3.2 Abstract

Background: Poor glycaemic control in patients with type 1 diabetes mellitus (Type 1 DM) is closely associated with an increased risk of microvascular complications. Our study aims to determine the mean retinal arteriolar and venular calibres at baseline visit, mid visit and final visit. We also look into the factors affecting the retinal vascular calibres in children with type 1 diabetes mellitus.

Methods: A cross-sectional prospective hospital-based study involving children with Type 1 DM. The participants were recruited from Ophthalmology and Paediatric Clinics of Universiti Sains Malaysia Hospital. Fundus photo of right eye were taken at baseline, mid and final visit and analyse by Singapore 1 Vessels Analysis (SIVA). HbA1c at each visit were documented.

Main Outcome Measure: Mean central arteriolar equivalent (CRAE) and venular equivalent (CRVE) were determined at each visit and its associated factors were analysed.

Results: The mean presenting age were 12.5 (2.24) years old. Majority of the participant were Malay race and mostly had poor glycaemic control at each visit. The mean CRAE and CRVE were not significantly differ between good and poor glycaemic group at each visit. However, the mean CRVE were significantly wider ($p=0.037$) in poor glycaemic control group along the duration of follow up. Age, duration of DM, blood pressure, BMI and HbA1c are not associated with vascular calibres.

Conclusion: A wider CRVE is associated with poorly glycaemic control DM. It can be one of earlier indicator in detecting the progression to diabetic retinopathy. In this closer and shorter duration of follow up study, no significant associated factors such as age, duration, blood pressure, BMI and glycaemic control with retinal vascular calibres.

Keyword: Type 1 DM, vascular calibres, glycaemic control, CRAE, CRVE

3.3 Introduction

The incidence of type 1 diabetes in children has been increasing worldwide[1-5] The average increase of type 1 diabetes cases are estimated to be 3-4% per year over past decades and a significant increment has been reported in a previously low-incidence countries.[6] The estimated incidence worldwide was 15 per 100 000 population and the prevalence of type 1 diabetes was 9.5 per 10 000 people.[7] International Diabetic Federation 2019 reported that the prevalence of Type 1 DM in Asia region were 184,100 cases with a total of 21,300 newly diagnosed cases per year.[1] A few studies in India, China and particularly Southeast Asia (Indonesia and Thailand) has also reported an increasing number of Type 1 DM in their countries.[8-12] In Malaysia, type 1 DM was estimated to account for 69.2% of children and adolescents with diabetes.[13]

Children with Type 1 DM were exposed to diabetes mellitus earlier in their life. Thus, we are anticipating more complications will occur in their later life such as macro angiopathies (eg: stroke, coronary heart disease and peripheral vascular disease) and micro angiopathies (eg: diabetic retinopathy, nephropathy and neuropathy). The glycaemic control is the key factor contributing to the development of diabetic complications. Many studies were done to demonstrate the relationship between the glycaemic control and complication of microangiopathy in Type 1 diabetes mellitus. A tight glycaemic control proven to reduce the complication of microangiopathy in patients with diabetes mellitus.[14-18]

By taking the fundus photography, the retinal vessels had been used to monitor changes in microvasculature geometry and calibres in diabetic patients. It is also considered as a non-invasive procedure and can be used as one of prognostic factor in predicting the chronic diabetes complications.[19-23] Studies has been performed to analyse the vascular calibre in type 1 DM and its association with glycaemic control.[24-26] In Singapore, Li et al reported a similar study in children with type 1 DM over one year observation.[26] However, there is limited data studies among children with type 1 DM in the developing Southeast Asian countries. Thus, we aim to describe the retinal vessels analysis by determining the central retinal arteriolar and venular calibres and its associated factors in Malaysian children with type 1 DM with a closer observation.