MICROVASCULAR CHANGES AND DIABETIC RETINOPATHY AND NEPHROPATHY PROGRESSION IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

Background: We established that the age at inception of T1DM significantly impacts the long-term risk of developing proliferative retinopathy in affected children and adolescents. Patients with T1DM, diagnosed before the age of 15 are at a significantly higher risk than children diagnosed at age 15 and older. For instance, several studies show changes in microangiopathy the first year of T1DM in children, suggesting that blood sugar changes may easily impact the retinal microvasculature. These changes have a significant impact on lifelong morbidity and mortality. Another target organ can be the kidney. Various studies disclose about thickening of glomerular basement membrane and expansion of the mesangium presented on kidney biopsy in young patients with T1DM. In children with T1DM, alterations in retinal blood vessels play a important role in progression of DR. Essential features of effective treatment plans include strict blood sugar control as well as regular screening to halt disease progression. New strategies offer an optimistic approach to optimizing retinal health and delaying vision loss.

To review studies conducted over the last ten years on microvascular changes and diabetic retinopathy and nephropathy in children and adolescents with T1DM. The review will also examine the diagnostic tools used, the results achieved, and the implications for current practice.

Methods: This brief literature review was conducted using electronic searches of authorized databases such as PubMed, Medline, and Google Scholar. We searched in the period from 2014 to 2024. We included the articles that focused on T1DM children and adolescents, reported sample sizes, used appropriate methods to measure microvascular changes, and provided sufficient descriptive and analytical data. We then organized the data into subtopics including microvascular changes, diagnostic methods, predisposing factors, and approaches to treating the disease.

Results: This work informs us about the association between age of onset of type 1 diabetes and the lifetime risk of diabetic retinopathy and nephropathy, which are serious complications.

Conclusion: It is important to detect microvascular changes and start appropriate treatments early in the development of DR in children and young adults with T1DM to prevent progression. Further research and development in this direction will help advance the understanding and treatment of T1DM.

Keywords: *T1DM, diabetic retinopathy, diabetic nephropathy, children, adolescents, retinal nerve fibre layer.*

Introduction

T1DM is an autoimmune disease that primarily affects children and adolescents. This type of diabetes mellitus affects the insulin-producing cells of the pancreas. This promotes the unconditional use of external insulin and constant control of blood sugar levels. Among the numerous known microvascular and neuropathic complications of T1DM, the most threatening are diabetic retinopathy and nephropathy, which can lead to blindness if neglected. DR is a long-term disease affecting the retinal microvasculature, and diabetic nephropathy affects glomerular mesangial cells. DR quickly

switches from NPDR to PDR due to complications such as macular oedema and retinal detachment, which can be very dangerous to the vision of young patients.

Microvascular changes appear to play a serious role in the development and progression of DR. These variations may occur very soon after the onset of T1DM and before the development of overt retinopathy. It is important to identify these microvascular changes in children and adolescents with T1DM to minimize the impact on vision and reduce the progression of severe vision loss. This study reviews the current literature on microvascular changes in retinal and mesangial cells and progression of DR in young patients with type 1 diabetes and evaluates new diagnostic tools, findings and their implications for clinical practice.

Microvascular Changes in T1DM

In children and adolescents with T1DM, some studies have reported first-order changes in microcirculation.(17) They have showed that changes in the appearance of retinal capillaries and neurons occurred even in teenagers with long-term T1DM, who did not clinically experience DR. GCL and IPL, part of the ganglion cell complex, were measured using OCT in young patients. The RNFL was thicker in non-DR than in DR patients, and in DR patients, the volume of the outer retina was increased. In this study, the researchers discovered that the changes in the outer retina were similar in both groups. Although the changes in the inner part of the retina have been studied in childhood T1DM patients, the changes in the outer part of the retina are not yet studied in young adults with this condition. There are various cell and organ components that contribute to the outer part of the retina, such as the photoreceptors and the Bruch's Membrane. (1) Researchers have discovered, that elevated cytokines activate microglia, thereby stimulating an inflammatory cycle that recruits leucocytes, causes vascular degradation and directly induces cell death through the release of cytotoxic substances. Higher levels of the two pro-inflammatory cytokines TNF-α and IL-1β contribute to thickening of BM. This supports the idea, that inflammation and metabolic disorders are the main causes of microvascular lesions in T1DM.

Li et al. (11) investigated the relationship between altered retinal microvasculature and inadequate glucose regulation. In this pilot study, 55 Singaporean children and teenagers with T1DM participated. They looked at the retinal vascular images both at baseline and a year later to see if there was any relationship between the glycaemic control and the linear dimension indices of the retinal arterioles. It was done using retinal photography. Two retinal images with the macula and optic disc in the centre were taken. The findings demonstrated that children and adolescents with an HbA1c of ≥ 8% had a wider retinal arteriolar segment and a higher arteriolar branching angle. This means that variations in blood glucose levels over a short period of time could be an indicator of the condition of retinal microcirculation and that the changes in retinal microvasculature associated with diabetes might appear in days as opposed to weeks.

The kidney is another potential target organ. The severe long-term consequence of type 1 diabetes known as diabetic nephropathy (DN) is characterized by an increase in arterial blood pressure, increasing proteinuria, and a steady reduction in kidney function. The presence of inflammation is indicated by elevated levels of interleukin-6 and C-reactive protein, which are predictive of diabetic nephropathy by patients with T1DM. The liver cells produce C-reactive protein (CRP), an acute-phase protein, in response to a variety of stimuli. It is also a highly accurate indicator of inflammation. Proinflammatory cytokines such as interleukin-6 (IL-6) are released by a variety of cells, including activated leucocytes, myocytes, endothelial cells, and adipocytes. Numerous research report the thickening of the glomerular basement membrane and expansion of the mesangium, observed during kidney biopsy in paediatric T1DM patients. Jong Baek et al (8) examined children and adolescents with T1DM. The disease lasted 14 years, with a 25-year-old median age at diagnosis. Lower levels of stimulated C-peptide were observed in individuals diagnosed with T1DM during childhood or adolescence (age <20 years). Compared to older onset groups, they received higher total

daily insulin doses and more intensive insulin treatment. When comparing older onset groups with childhood/adolescent onset groups, the prevalence of DN was higher in the former (25,3% versus 15,3% P = 0, 022). While the degree of decline was more pronounced in the childhood/adolescent onset group than in the later-onset group (aged 30 to 40 years; P<0.001), eGFR was inversely correlated with disease duration. They conclude that the reduction in renal function in patients with childhood type 1 diabetes becomes more evident as the disease progresses. In addition, patients with type 1 diabetes are more likely to develop end-stage renal disease from chronic kidney disease and this is in T1DM patients closely linked to cardiovascular disease.

Studies of microvascular changes in young patients with T1DM show early changes before clinical complications occur. Endothelial dysfunction, characterized by decreased flow-mediated dilation (FMD), is associated with microvascular complications in T1DM patients.

Mesangial cells in diabetic nephropathy exhibit changes in gene expression related to the extracellular matrix, cell division, and growth factor modulation (4). Glomerular morphometry studies show progression of mesangial volume fraction and glomerular basement membrane width with increasing disease duration (9).

In order to assess the critical mesangial and basement membrane morphometric changes characteristic of diabetic nephropathy, Drummond et al. report findings from the International Diabetic Nephropathy Study, which circumvents the majority of these methodologic issues by obtaining kidney biopsies on type 1 diabetic subjects prior to the onset of microalbuminuria (13). Comprehensive data on blood pressure, BMI, Tanner staging, and glycaemic control (glycosylated haemoglobin) are accessible upon study enrolment. Furthermore, researchers have employed statistical techniques that disentangle the impact of the disease's overall duration from that of the age at onset. Microcirculatory changes in children with T1DM include reduced glycocalyx thickness, which is inversely correlated with blood glucose levels, and increased large vessel proportion at the expense of capillaries (16). These results suggest that early detection of microvascular changes, particularly in the glycocalyx, may provide opportunities for earlier interventions and new therapeutic strategies in the treatment of diabetic microangiopathy.

Tools for Diagnosing and Monitoring

Different clinical practice guidelines have been developed for ophthalmic screening in adolescents with type 1 diabetes as a result, though the recommended timing of monitoring varies among medical societies. According to the American Academy of Ophthalmology (AAO), the first screening should be done five years after the onset of T1DM. There should be an initial screening three to five years after T1DM onset for patients ten years of age or older, according to the American Diabetes Association (ADA) and the American Academy of Paediatrics (AAP). Delaying the first eye exam until the age of 15 is reasonable, as stated by a recent study. These guidelines all suggest optimizing diabetes management as determined by the glycated haemoglobin fraction (HbA1c).

In T1DM, better imaging can demonstrate dynamic alterations to microvascular conditions. Two techniques, OCTA and fundus photography, respectively, perform the structural and microvascular retinal assessments. In the study by Mohd-Ilham et al. (14) is utilized SD-OCT’s capacity to establish macular and RNFL thickness differences in diabetic and non-diabetic children. The findings revealed that children with T1DM had reduced macular and RNFL thickness compared to the control group, thereby affirming the importance of OCT in the early detection of retinopathy among the diagnosed child patients.

In the study by Scarinci et al (18), OCTA evaluated some parameters including PVD and FAZ area. Both areas are essential for calculating microvascular density and health. To classify indicators of microvascular changes that indicate DR development in children with T1DM, the specialists slowly measured the parameters at numerous time points during the patients' two-year follow-up period.

Because of this, it is beneficial and possible to use OCTA to measure microvascular limits, as well as other methods for diagnosing DR and checking on its progression in young patients with T1DM. Hence, by measuring these biomarkers, medical professionals can detect the advancement of DR at an early stage and implement appropriate interventions that can lower the likelihood of vision-threatening issues in these patients.

The International Society for Paediatric and Adolescent Diabetes guidelines state that annual microalbuminuria, or urine protein screening, should be carried out beginning at age 11 and every year after the onset of diabetes for the first two years. Sustained microalbuminuria is linked to a higher risk of macrovascular complications and has been demonstrated to predict the course of end-stage renal disease. Urine microalbumin creatinine ratio (UACR) monitoring in paediatric T1DM patients should start at puberty or age ten. This should be checked every year if the child has had DM for five years. UACR should be evaluated for T2DM both at diagnosis and yearly after that. The widely used and still considered "gold standard" marker in medical practice for identifying and forecasting diabetic kidney involvement in paediatric diabetes is microalbuminuria screening.

Risk Factors and Associations

Some factors determine the development of microvascular modifications and the presence of DR and DN in patients with T1DM in childhood and adolescence. Frequent studies also show that poor glycaemic control is the main risk factor. For example, Chen et al. (3) observed in their study that children with poor blood sugar control had meaningfully narrow retinal vessels and increased vascular tortuosity, both of which are indicators of DR. In particular, hypertension and dyslipidaemia are the factors that influence microvascular function and progression of DR and DN.

Researchers have also found a direct link between the duration of diabetes and the occurrence of hypoglycaemia (7;8). According to Kernell (7) the incidence of DR increased with diabetes duration and pubertal growth. A highlight of this work is the early inclusion of children and adolescents in DR screening programs, especially those with a longer duration of illness.

Management Strategies

The Diabetes Control and Complication Trial (DCCT) has long permitted intensive insulin therapy as an effective method for reducing the risk of DR. In addition to glucose, blood pressure and lipids are other notable factors that cause microvascular complications.

New therapies to treat microvascular dysfunction have the potential to be beneficial. Researchers are also testing anti-VEGF agents, typically used in adult DR treatment. In addition, treatment with neuroprotective and anti-inflammatory agents may play a role in maintaining retinal function in children and adolescents with T1DM (12). For instance, new studies show that interventions that reduce the release of VEGF and provocative cytokines can stop the progression of DR by reducing ischemic vessel damage and inflammation.

Screening for DR and DN and classifying them in their early stages are important parts of proper diabetes management.

Findings and Results

This article educates us about the association between beginning of T1DM and the lifetime risk of PDR and DN the most serious complications of the disease. For the study, researchers used data from the FinnDiane study population, 1,117 patients with T1DM, and analysed the age of onset and development of proliferative retinopathy over time. The different age groups showed differences in the characterization of the risk of proliferative retinopathy. Wright and Hirsch (20) observed that patients aged 5 to 14 years, diagnosed with T1DM had a risk ratio of 1.90 (95% CI 1.45–48), compared to those diagnosed patients at highest risk of developing proliferative retinopathy, were at other ages. Specifically, they found no gender difference in the 4-year cumulative incidence of any

degree of retinopathy: 14% in men and 12% in women. In further analysis, patients were divided into two large groups by age of onset: <15 years and ≥15 years: The results showed that adolescents diagnosed with T1DM before the age of 15 had a significantly higher risk, in the longer period of PDR complications, which is associated with a risk rate of 1.82 (95% CI 1.40–2.36), compared to those diagnosed at other ages.

These outcomes lead to the conclusion that AAO is the determinant of the course of treatment of DR in children and adolescents with T1DM. Though it was also established that the highest risk level of proliferative retinopathy was in subjects diagnosed with the condition in the age range of 5–14 years, but increased long-term risk was evident, whether the patients were diagnosed before or after 15 years of age.

C. Muntean (15) examined all tools for early detection of diabetic kidney disease in children and adolescents with type 1 diabetes, including limitations of microalbuminuria and the potential of tubular biomarkers for diagnosis. DKD, the most significant and common burden of this metabolic disorder, is still detected late because microalbuminuria is the most commonly used biomarker to predict renal involvement. Novel biomarkers are valuable tools for detecting kidney damage in early phases and reliable predictors of DKD progression. Therefore, effective therapies can be suggested. Early prediction and detection of DKD in children and adolescents before the onset of microalbuminuria plays a crucial role in preventing the development and/or progression of irreversible kidney damage, as well as in timely treatment and appropriate management through the use of conventional and novel therapies that can slow the onset or progression of DKD.

Conclusion

Children and young adults with T1DM primarily see changes in their vision. This study also supported previous evidence that shows poor glycaemic control, hypertension, dyslipidaemia, and a long duration of diabetes as possible outcomes that may cause microvascular changes and DR and DN. Therefore, to halt the development of DR and DN, we need to incorporate pharmacological therapies that are associated with stricter glycaemic control, blood pressure, lipid profiles, and regular screening.

Abbreviations: BM-basement membrane; T1DM-type 1 diabetes mellitus; DR-diabetic retinopathy; DN-diabetic nephropathy; CRP- C-reactive protein; DKD-diabetes kidney disease

References

1. Bianchi, E., Ripandelli, G., Taurone, S., Feher, J., Plateroti, R., Kovacs, I., Magliulo, G., Orlando, M. P., Micera, A., Battaglione, E., & Artico, M. (2016). Age and diabetes related changes of the retinal capillaries: An ultrastructural and immunohistochemical study. International Journal of Immunopathology and Pharmacology, 29(1), 40–53. https://doi.org/10.1177/0394632015615592
2. Muntean C, Starcea IM, Banescu C. Diabetic kidney disease in pediatric patients: A current review. World J Diabetes 2022; 13(8) https://doi.org/10.4239/wjd.v13.i8.587
3. Chen, S., Xiao, Y., Cui, L., Qin, X., An, Q., Yuan, T., Wu, Y., Lin, Q., Qian, Y., Yang, C., & Zou, H. (2024). Three-year follow-up study investigating changes in retinal vascular morphology and the relationship with diabetic retinopathy in children with type 1 diabetes mellitus. Ophthalmic Research. https://doi.org/10.1159/000538797
4. Eric W Brunskill and S Steven Potter. (2012) Changes in the gene expression programs of renal mesangial cells during diabetic nephropathy. BMC Nephrology 13:70 https://doi.org/10.1186/1471-2369-13-70
5. Harrison, W. W., Bearse, M. A., Schneck, M. E., Wolff, B. E., Jewell, N. P., Barez, S., Mick, A. B., Dolan, B. J., & Adams, A. J. (2011). Prediction, by Retinal Location, of the Onset of Diabetic Edema in Patients with Nonproliferative Diabetic Retinopathy. Investigative Opthalmology & Visual Science, 52(9), 6825. https://doi.org/10.1167/iovs.11-7533

6. Hletala, K., Harjutsalo, V., Forsblom, C., summanen, P., & Groop, P.-H. . (2010). Age at Onset and the Risk of Proliferative Retinopathy in Type 1 Diabetes. Diabetes Care, 33(6), 1315–1319. https://doi.org/10.2337/dc09-2278
7. Kernell, A., Dedorsson, I., Johansson, B., Wickström, C. P., Ludvigsson, J., Tuvemo, T., Neiderud, J., Sjöström, K., Malmgren, K., Kanulf, P., Mellvig, L., Gjötterberg, M., Sule, (1997) Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study. Diabetologia 1997 Mar;40(3):307-10 https://doi.org/10.1007/s001250050679
8. Jong Baek, Woo Je Lee, Byung-Wan Lee et al(2021) Age at diagnosis and the risk of diabetic nephropathyin young patients with type 1 diabetes mellitus. Diabetes Metab J 2021 45-54 https://doi.org/10.4093/dmj.2019.0134
9. K. Drummond, M. Kramer, S. Suissa, C. Lévy-Marchal, S. Dell'aniello, A. Sinaiko, M. Mauer (2003) Effects of duration and age at onset of type 1 diabetes on preclinical manifestations of nephropathy. Diabetes journal https://doi.org/10.2337/DIABETES.52.7.1818
10. J., Persson, L. A., Larsson, L. I., Aman, J., & Dahlquist, G. (1997). Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study. Diabetologia, 40(3), 307–310. https://doi.org/10.1007/s001250050679
11. Li, L.-J., Lamoureux, E., Wong, T. Y., & Lek, N. (2017). Short-term poor glycemic control and retinal microvascular changes in pediatric Type 1 Diabetes patients in Singapore: a pilot study. BMC Ophthalmology, 17(1). https://doi.org/10.1186/s12886-017-0449-8
12. Mayer-Davis, E. J., Davis, C., Saadine, J., D'Agostino, R. B., Dabelea, D., Dolan, L., Garg, S., Lawrence, J. M., Pihoker, C., Rodriguez, B. L., Klein, B. E., & Klein, R. (2012). Diabetic retinopathy in the SEARCH for Diabetes in Youth Cohort: a pilot study. Diabetic Medicine, 29(9), 1148–1152. https://doi.org/10.1111/j.1464-5491.2012.03591.x
13. Mauer M, Drummond K, for the International Diabetic Nephropathy Study Group: The early natural history of nephropathy in type 1 diabetes. I. Study design and baseline characteristics of the study participants. Diabetes 51:1572–1579,2002 https://doi.org/10.2337/diabetes.51.5.1572
14. Mohd-Ilham, I., Tai, E. L. M., Suhaimi, H., & Shatriah, I. (2021). Evaluation of Macular and Retinal Nerve Fiber Layer Thickness in Children with Type 1 Diabetes Mellitus without Retinopathy. Korean Journal of Ophthalmology: KJO, 35(4), 287–294. https://doi.org/10.3341/kjo.2020.0106
15. Muntean C, Starcea IM, Banescu C. Diabetic kidney disease in pediatric patients: a current review. World J Diabetes. 2022;13 587–99. https://doi.org/10.4239/wjd.v13.i8.587
16. C. Nussbaum, Ana Cavalcanti Fernandes Heringa. (2014) Early microvascular changes with loss of the glycocalyx in children with type 1 diabetes. Jornal de Pediatria https://doi.org/10.1016/j.jpeds.2013.11.016
17. Pilotto, E., Torresin, T., Leonardi, F., Gutierrez De Rubalcava Doblas, J., Midena, G., Moretti, C., & Midena, E. (2022). Retinal Microvascular and Neuronal Changes Are Also Present, Even If Differently, in Adolescents with Type 1 Diabetes without Clinical Diabetic Retinopathy. Journal of Clinical Medicine, 11(14), 3982. https://doi.org/10.3390/jcm11143982
18. Scarinci, F., Picconi, F., Virgili, G., Varano, M., Giorno, P., Frontoni, S., & Parravano, M. (2020). Microvascular impairment as a biomarker of diabetic retinopathy progression in the long-term follow up in type 1 diabetes. Scientific Reports, 10(1), 18266. https://doi.org/10.1038/s41598-020-75416-8
19. Seon Mi Jin, C. Noh, S. Yang, E. Bae, C. Shin, Hae Rim Chung, You Yeh Kim, Y. Yun (2008). Endothelial Dysfunction and Microvascular Complications in Type 1 Diabetes Mellitus. The Korean Academy of Medical Sciences;23(1):77-82. https://doi.org/10.3346/jkms.2008.23.1.77
20. Wright, L. A.-C., & Hirsch, I. B. (2017). Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. Diabetes Technology & Therapeutics, 19(S2), 16-26. https://doi.org/10.1089/dia.2017.0029