Changes in Retinal Ganglion Cell (RGC) and Retinal Nerve Fiber Layer (RNFL) Thickness in Children with Type 1 Diabetes Mellitus at Dr. M. Djamil General Hospital, Padang, Indonesia

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ABSTRACT

Background: Type 1 diabetes mellitus (DM) is a chronic metabolic disorder that causes hyperglycemia and increases the risk of morbidity and mortality. Diabetic retinopathy, a microvascular complication that often occurs in DM patients, can cause visual impairment and even blindness. Regular eye examinations are important for early detection of diabetic retinopathy. Optical coherence tomography (OCT) is a non-invasive method that can be used to measure the thickness of retinal layers, including RGC and RNFL. It is thought that thinning of the retinal layer can be a sensitive biomarker in detecting diabetic retinopathy in type 1 DM patients. This study aims to determine changes in RGC and RNFL thickness in children with type 1 DM.

Methods: This cross-sectional design analytical observational study was conducted at the eye polyclinic of Dr. M. Djamil General Hospital Padang in November 2023-March 2024. A total of 46 eyes from 46 people, divided into two groups: the type 1 DM group and the control group, were recruited in this study. RGC thickness was measured using AS-OCT GC-IPL thickness analysis and RNFL with optic disc RNFL thickness analysis. Data analysis was carried out using the unpaired T-test. Results: The results showed RGC depletion in the type 1 DM group (RGC 83.48 ± 3.75) compared to the control group (RGC 86.70 ± 4.87) with a value of p = 0.016 (p < 0.05). There was no statistical difference in RNFL thickness between the type 1 DM group (RNFL 102 ± 11.80) and the control group (RNFL 100.96 ± 10.97) with a value of p = 0.581 (p> 0.05). Conclusion: This study found RGC thinning in type 1 DM patients, but did not find differences in RNFL thickness between the two groups. This RGC depletion is thought to be caused by apoptosis of retinal neuronal cells due to chronic hyperglycemia. Examination of RGC thickness with OCT can be developed as an early detection of diabetic retinopathy in children with type 1 DM.

1. Introduction

Diabetes mellitus (DM) type 1 is a chronic metabolic disease characterized by persistent hyperglycemia due to absolute or relative insulin deficiency. This disease knows no age, and unfortunately, the prevalence of type 1 DM in children and adolescents is quite worrying. In Indonesia, it is estimated that 0.2 out of every 100,000 children suffer from type 1 DM. Compared to type 2 DM which generally attacks adults, type 1 DM is more complex and requires more intensive treatment. Chronic hyperglycemia in type 1 DM patients can cause various serious complications, including diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease. Diabetic retinopathy is the most common microvascular complication in DM
patients and is the main cause of blindness in working-age adults in developed countries. In children with type 1 DM, diabetic retinopathy can progress more quickly and be more severe than in adults. Chronic hyperglycemia in DM patients causes damage to the retinal blood vessels, which triggers various pathological processes such as microaneurysms, bleeding, exudation, and proliferation of new blood vessels. This damage slowly disrupts the function of the retina and leads to a decrease in the quality of vision, even blindness.1-3

Early detection of diabetic retinopathy is very important to prevent blindness and other complications. Routine eye examinations, at least annually, should be performed on all children with type 1 DM. Funduscopic examination, which is a standard eye examination, can detect diabetic retinopathy at an early stage. However, fundoscopy has limitations in detecting microscopic changes in the retina. This is where optical coherence tomography (OCT) comes in as a more sophisticated solution. OCT is a non-invasive optical imaging method that allows detailed visualization of retinal structures with high resolution. OCT can measure the thickness of retinal layers, including the retinal ganglion cell layer (RGC) and retinal nerve fiber layer (RNFL). Research shows that RGC and RNFL thinning can be sensitive biomarkers in detecting diabetic retinopathy in type 1 DM patients. This thinning is thought to be caused by apoptosis of retinal neuronal cells due to chronic hyperglycemia. Although previous studies have shown mixed results, RGC and RNFL thinning could potentially be an early indicator of diabetic retinopathy in children with type 1 DM.4-6 This study aims to determine changes in RGC and RNFL thickness in children with type 1 DM at Dr. M. Djamil General Hospital, Padang, Indonesia.

2. Methods

This research uses an analytical observational design with a cross-sectional approach. This design was chosen to analyze the relationship between the independent variable (DM type 1) and the dependent variables (RGC and RNFL thickness) at a specific point in time. This research was conducted at the eye polyclinic of Dr. M. Djamil General Hospital, Padang in the period November 2023 to March 2024. The research sample consisted of 46 eyes from 46 people who were divided into two groups: 1. Type 1 DM group: consisting of 23 people with a confirmed diagnosis of type 1 DM. 2. Control group: consisting of 23 people without DM and no other risk factors for DM. The inclusion criteria for this study were a minimum age of 6 years and a maximum of 18 years, having a confirmed diagnosis of type 1 DM, not having other eye diseases that could affect retinal thickness, and being willing to participate in the research and provide informed consent. Meanwhile, the exclusion criteria are a history of eye surgery, eye trauma, eye infections, vision problems that are not related to DM. This research was approved by the health research ethics committee of Dr. M. Djamil General Hospital, Padang. Informed consent was obtained from all participants before the study was conducted. All patient data is kept confidential and is only used for research purposes.

Research data was collected through: 1. Interview: Used to obtain demographic information and patient medical data, including DM history, DM treatment, and other DM complications. 2. Eye examination: Performed to measure RGC and RNFL thickness using the optical coherence tomography (OCT) method. 3. Blood pressure and blood glucose measurements: Performed to monitor the patient’s glycemic control status. RGC thickness was measured using the AS-OCT GC-IPL thickness analysis method. This method uses a laser beam to scan the retina and produce detailed cross-sectional images. RGC thickness was measured in nine different retinal areas. RNFL thickness was measured using the optic disc RNFL thickness analysis method. This method also uses a laser beam to scan the retina and produce detailed cross-sectional images. RNFL thickness was measured in a circle around the optic nerve papilla. Research data were analyzed using the unpaired T-test to compare RGC and RNFL thickness between the type 1 DM group and the control group.
DM group and the control group. This statistical test is used to determine whether there are significant differences between the two groups.

3. Results

Table 1 presents the characteristics of study respondents who were divided into two groups: patients with type 1 diabetes mellitus (Type 1 DM) and the control group. The average age of respondents in the two groups was close, with the type 1 DM group aged 13 ± 1.94 years and the control group aged 14 ± 1.7 years. This age difference was not statistically significant (p=0.476). Comparable age of respondents in both groups helps reduce bias in data analysis because the possible influence of age on research variables can be minimized. The type 1 DM group had a smaller proportion of men (30.4%) than the control group (43.5%). However, this difference was not statistically significant (p=0.359). A balanced gender proportion in both groups helps ensure that the study results are not influenced by gender factors. Most respondents with type 1 DM had suffered from this disease for more than 3 years (60.9%), while the remainder (39.1%) had type 1 DM of less than 3 years. Information about the duration of type 1 DM can help in the interpretation of study results, especially in relation to changes in retinal structure that may occur as the disease progresses. Most respondents with type 1 DM had HbA1C levels above 7.5 mg/dL (82.6%), which indicates less than optimal glycemic control. Only 4 respondents (17.4%) had HbA1C levels below 7.5 mg/dL, which is the ideal glycemic control target for DM patients. Information about HbA1C levels can help in understanding the severity of type 1 DM in respondents and its potential influence on changes in retinal structure. Analysis of the characteristics of the study respondents showed that the two groups had comparable demographic characteristics, which can help reduce bias in data analysis. Information about the duration of type 1 DM and HbA1C levels in the type 1 DM group can provide an overview of the patient's condition and help in the interpretation of research results.

<table>
<thead>
<tr>
<th></th>
<th>Type 1 DM (n=23)</th>
<th>Control (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (year)</td>
<td>13 ± 1.94</td>
<td>14 ± 1.7</td>
<td>0.476</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (30.4%)</td>
<td>10 (43.5%)</td>
<td>0.359</td>
</tr>
<tr>
<td>Female</td>
<td>16 (69.6%)</td>
<td>13 (56.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of type 1 DM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 Years</td>
<td>9 (39.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 Years</td>
<td>14 (60.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1C levels</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.5 mg/dL</td>
<td>4 (17.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7.5 mg/dL</td>
<td>19 (82.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 presents the results of research on RGC and RNFL thickness in the type 1 DM group and controls. The results showed that there was a statistically significant difference in RGC thickness between the type 1 DM group (83.48 ± 3.75 μm) and the control group (86.70 ± 4.87 μm). The p-value (0.016) indicates that this difference is large enough to be considered statistically significant (p<0.05). There was no statistically significant difference in RNFL thickness between the type 1 DM group (102.00 ± 11.80 μm) and the control group (100.96 ± 10.97 μm). The p-value (0.581) indicates that the observed
difference is not large enough to be considered statistically significant ($p>0.05$). This study shows that RGC depletion can be an early biomarker of diabetic retinopathy in children with type 1 DM. These findings support the importance of routine eye examinations in children with type 1 DM for early detection of diabetic retinopathy and early intervention to prevent blindness.

**Table 2. The thickness of RGC and RNFL in type 1 DM and control groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 1 DM group ($n=23$)</th>
<th>Control group ($n=23$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RGC thickness (µm)</td>
<td>83.48 ± 3.75</td>
<td>86.70 ± 4.87</td>
<td>0.016</td>
</tr>
<tr>
<td>RNFL thickness (µm)</td>
<td>102.00 ± 11.80</td>
<td>100.96 ± 10.97</td>
<td>0.581</td>
</tr>
</tbody>
</table>

**4. Discussion**

One type of nerve cell that plays an important role in vision is the retinal ganglion cell layer (RGC). RGCs are like a bridge that connects the outside world with our brain, translating visual information into signals that the brain can understand. RGCs are located in the inner retina, specifically in the ganglion layer. The retina is like a camera in our eyes, capturing light and converting it into electrical signals. Photoreceptors, light-sensitive cells in the retina, detect light and send electrical signals to the RGCs. RGCs then process these signals, integrating information from various photoreceptors to form a coherent visual image. Next, the RGC sends the processed signal to the brain via the optic nerve, like a cable that connects the eye to the brain. Depletion of RGCs, such as damage to cell bridges, can disrupt the smooth passage of visual information. When the number of RGCs decreases, the eye’s ability to process and transmit visual information to the brain also decreases. This can result in various vision problems. The ability to see fine details is reduced, such as reading small text or seeing objects from a distance. Difficulty distinguishing objects from their background, especially in low lighting conditions. Loss of some areas of vision, such as the top, bottom or sides. In severe cases, extreme RGC depletion can lead to complete blindness. RGC thinning is not just a vision problem, but is also a potential indicator of more extensive nerve damage to the retina. The retina contains various other types of nerve cells that work together to produce clear vision. Damage to RGCs can be an early sign of damage to other nerve cells in the retina, increasing the risk of serious eye complications such as diabetic retinopathy and glaucoma. Preventing and treating conditions that can cause RGC depletion, such as diabetes and glaucoma, is critical to maintaining healthy eyes and vision. Regular eye exams, good blood sugar control, and a healthy lifestyle can help protect RGCs and keep our vision clear. RGCs play an important role in vision, connecting the outside world with our brain via the optic nerve. RGC thinning can cause a variety of vision problems and is a potential indicator of more extensive nerve damage to the retina. Keeping RGCs healthy by preventing and treating conditions that can cause their damage is essential to maintaining clear, healthy vision.7–9

Hyperglycemia, chronic high blood sugar levels in diabetes patients, is like poison to the retina, the eye organ responsible for vision. One way hyperglycemia damages the retina is by increasing the production of oxygen free radicals (ROS). ROS are like mini bombs that can damage retina cells, including RGC (retinal ganglion cell layer). ROS are reactive molecules that contain oxygen. Under normal conditions, ROS are produced in small amounts and play a role in various cellular processes. However, in diabetes patients, hyperglycemia triggers excessive ROS production, like a free radical storm that destroys retina cells. ROS can attack DNA inside RGC cells, causing mutations and errors in DNA replication. This can disrupt the normal function of RGCs and even trigger cancer. ROS can modify proteins within RGC cells, changing their structure and rendering them non-functional. These damaged proteins can accumulate and disrupt important cellular processes. ROS can attack RGC cell
membranes, causing leakage and loss of normal cell function. Severe cell membrane damage can trigger apoptosis (cell death) of RGCs. Apoptosis is a programmed and controlled process of cell "suicide". Under normal conditions, apoptosis plays an important role in maintaining the balance of the number of cells in the body. However, in RGCs, hyperglycemia and excessive ROS can trigger uncontrolled apoptosis, leading to massive RGC cell death.\textsuperscript{10-12}

Hyperglycemia in diabetes patients not only increases ROS production, but also triggers a chronic inflammatory storm in the retina. This storm produces inflammatory mediators such as cytokines and chemokines, which are like mercenaries that damage retinal cells and disrupt RGC function. Hyperglycemia can activate various inflammatory pathways in the retina. These pathways involve various inflammatory cells, such as macrophages and microglia, which produce inflammatory mediators. These inflammatory mediators have various damaging effects on retinal cells. Inflammatory mediators can trigger apoptosis (cell death) of RGCs through various mechanisms, such as oxidative stress and activation of cell death pathways. Inflammatory mediators can damage the structure of retinal tissue, including blood vessels and cell membranes, which can disrupt blood flow and RGC function. Inflammatory mediators can interfere with the production and release of neurotrophics, such as BDNF (brain-derived neurotrophic factor), which are important for RGC survival and function. Chronic inflammation in the retina due to hyperglycemia can cause various problems in RGCs. RGC death due to inflammation can lead to RGC depletion, resulting in decreased visual acuity and other vision problems. Inflammation can disrupt RGC function, such as its ability to process and transmit visual information to the brain. Chronic inflammation can contribute to the development of diabetic neuropathy, which is nerve damage in diabetes patients. Preventing and controlling hyperglycemia is an important step to calm the inflammatory storm in the retina and protect RGCs from damage. Effective diabetes treatment and a healthy lifestyle can help lower blood sugar levels and reduce activation of inflammatory pathways. Additionally, anti-inflammatory therapies that target specific inflammatory mediators may help reduce inflammation in the retina and protect RGCs from damage. Hyperglycemia in diabetic patients triggers a chronic inflammatory storm in the retina, which produces inflammatory mediators that damage retinal cells and disrupt RGC function. This chronic inflammation can lead to RGC depletion, RGC dysfunction, and diabetic neuropathy. Preventing and controlling hyperglycemia through diabetes treatment and a healthy lifestyle, as well as anti-inflammatory therapy, is essential to protect RGCs from damage caused by inflammation and maintain clear vision.\textsuperscript{13-16}

Hyperglycemia in diabetes patients not only triggers direct retinal cell damage but can also cause damage to the retinal blood vessel endothelium, like damage to a water pipe that disrupts the flow of water to the house. This damage can cause hypoxia and nutritional deficiencies in RGCs, which ultimately triggers apoptosis (cell death). The endothelium is a thin layer of cells that lines the inside of the retina’s blood vessels. The endothelium has various important functions. The endothelium produces substances that help keep blood flow smoothly and prevent blood clots. The endothelium controls the movement of substances between the blood and surrounding tissue, ensuring that nutrients and oxygen can reach the retina cells. The endothelium produces anti-inflammatory and antioxidant substances that help protect the retina from damage. Hyperglycemia can damage the retinal blood vessel endothelium through various mechanisms. Hyperglycemia increases the production of ROS, which can damage endothelium cells and disrupt their function. Hyperglycemia triggers the activation of chronic inflammatory pathways, which produce inflammatory mediators that can damage endothelium cells. Hyperglycemia can cause protein glycation, which is the process of attaching sugar to protein. Protein glycation on endothelium proteins can
disrupt their function. Damage to the retinal vascular endothelium due to hyperglycemia can cause various problems in RGCs. Damage to the endothelium can disrupt blood flow to the retina, causing hypoxia (lack of oxygen) in the RGCs. Hypoxia can disrupt the normal function of RGCs and even trigger apoptosis. Damage to the endothelium can also disrupt the movement of nutrients from the blood to the retina, causing nutritional deficiencies in RGCs. Lack of these nutrients can disrupt the normal function of RGCs and even trigger apoptosis. Hypoxia and nutritional deficiencies resulting from damage to the endothelium can lead to RGC dysfunction, such as a reduction in their ability to process and transmit visual information to the brain. Preventing and controlling hyperglycemia is an important step to protect the retinal vasculature from damage and ensure smooth blood flow to the RGCs. Effective diabetes treatment and a healthy lifestyle can help lower blood sugar levels and reduce damage to the endothelium. Additionally, therapies that target endothelium damage, such as antioxidant therapy and anti-inflammatory therapy, may help protect retinal vasculature and maintain smooth blood flow to RGCs.\textsuperscript{16-18}

Hyperglycemia in diabetic patients not only directly damages RGCs but can also disrupt neurotrophic production and release, such as shutting off water flow that is important for keeping plants alive. Neurotrophics, such as brain-derived neurotrophic factor (BDNF), are important for RGC survival and function. A lack of neurotropho may increase the susceptibility of RGCs to apoptosis (cell death). Neurotrophics are proteins that play an important role in the growth, survival and function of neurons, including RGCs. Neurotrophics work by binding to specific receptors on the surface of neurons, triggering various important cellular processes. Neurotrophic helps neurons grow and develop into mature form and function. Neurotrophic protects neurons from apoptosis and helps them survive under stressful conditions. Neurotrophic increases the ability of neurons to form new connections and strengthen existing ones, which is important for learning and memory. BDNF is one of the most important neurotrophic agents for RGCs. BDNF helps RGCs grow and develop into mature neurons with strong neural connections. BDNF protects RGCs from apoptosis and helps them survive stressful conditions, such as oxidative stress and inflammation. BDNF increases the ability of RGCs to process and transmit visual information to the brain. Hyperglycemia can interfere with the production and release of neurotrophics, including BDNF. Hyperglycemia increases ROS production, which can damage retinal cells and disrupt neurotrophic production. Hyperglycemia triggers the activation of chronic inflammatory pathways, which can disrupt neurotrophic production and release. Hyperglycemia can disrupt cellular signaling pathways involved in neurotrophic production. Lack of neurotrophy due to hyperglycemia can cause various problems in RGCs. A lack of neurotrophy may increase the susceptibility of RGCs to apoptosis, which may lead to RGC depletion. A lack of neurotrophy can disrupt RGC function, such as its ability to process and transmit visual information to the brain. Neurotrophic disorders may contribute to the development of diabetic neuropathy, which is nerve damage in diabetes patients. Preventing and controlling hyperglycemia is an important step to maintain normal neurotrophic production and release and protect RGCs from damage. Effective diabetes treatment and a healthy lifestyle can help lower blood sugar levels and reduce neurotrophic disorders. Additionally, therapies that stimulate neurotrophic production, such as gene therapy and cell therapy, may help increase neurotrophic levels in the retina and protect RGCs from damage. Hyperglycemia in diabetic patients can disrupt the production and release of neurotrophics, such as BDNF, which are important for RGC survival and function. A lack of neurotrophy may increase the susceptibility of RGCs to apoptosis and lead to various problems, such as RGC depletion, RGC dysfunction, and diabetic neuropathy. Preventing and controlling hyperglycemia through diabetes treatment and a healthy lifestyle, as well as therapies that stimulate neurotrophic...
production, are critical to protecting RGCs from damage and maintaining clear vision.\textsuperscript{17-20}

5. Conclusion
The findings of this study indicate that there is a depletion of RGCs in children with type 1 DM. This thinning can be caused by apoptosis of retinal neuronal cells due to chronic hyperglycemia in type 1 DM patients. Hyperglycemia can trigger oxidative stress, chronic inflammation, and disruption of retinal blood flow, which ultimately causes damage to retinal cells, including RGCs. This study also shows that measuring RGC thickness can be an effective method for early detection of diabetic retinopathy in children with type 1 DM. RGC thinning can be an early indicator of retinal damage due to DM and can help in monitoring disease progression.

6. References
