Introduction

The prevalence of type 2 diabetes mellitus (DM) has increased markedly in Asian countries and more than 60% of global diabetic population [1]. DM is an important health problem that induces complications and it causes significant morbidity due to specific microvascular complications such as retinopathy, nephropathy, and neuropathy [2, 3].

According to the latest International Diabetes Federation (IDF) figures, there are currently 463 million people living with DM and the total is expected to rise 700 million by 2045. In Indonesia, according to IDF there are 9.1 million people living with DM in 2014 and total is expected to rise 14.1 million in 2035. Vascular complications will affect autoregulation of the retina and optic nerves, causing reduced blood flow to the eye, and impaired oxygen dysfunction to the eye. This condition caused hypoxia and ischemic damage to the ganglion cells and the optic nerve which results in glaucoma [4], [5], [6].

Glucomatous optic neuropathy is characterized by progressive loss of retinal ganglion cells and their axons and lead to measurable structural and functional damage to optic nerve, visual impairment, and elevated intraocular pressure (IOP) are one of the primary risk factor [7]. Glaucoma is one of the leading cause of worldwide irreversible blindness [8]. By year 2020, it is estimated that worldwide prevalence of glaucoma will approach 80 million being bilaterally blind from glaucoma. In Indonesia, based on the results of Riset Kesehatan Dasar, the prevalence of glaucoma in 2007 was 0.5% and according to an eye health survey by the Ministry of Health of Republic Indonesia in 1993–1996, it shows glaucoma was the second cause of blindness after cataract estimated 0.2% [9], [10].

It has not been determined definitely whether there is a significant association between DM and glaucoma. Some population based study has shown a positive association between DM and glaucoma, and other hands have shown negative association between DM and glaucoma. However, in many studies...
that showed a lack of a significant association between diabetes and glaucoma [11], [12]. Some authorities believe that small-vessel involvement in diabetes may cause the optic nerve to become more susceptible to pressure-related damage but it is not known whether variations in glucose levels could lead IOP changes [12].

Hyperglycemic conditions in DM cause structural damage to the endothelium and retinal blood vessel tight junctions which can lead to increased systolic blood, microalbuminuria, and lipid profile. Patients with DM have lipid profiles that appear more benign than those other high risk people without diabetes [13], [14]. But in fact, the most common low-density lipoprotein cholesterol (LDL-C) level in DM is “borderline high” (130–159 mg/dl). This condition can initiate atherosclerotic and apoptosis vascular smooth muscle in existing atherosclerotic lesions [14]. Several studies reported a correlation between serum lipids and the incidence of glaucoma, but the correlation between glycemic control and serum lipids with glaucomatous optic neuropathy in patients with type 2 diabetes has never been found. As the diabetes and glaucoma coexist in many patients, we though to analyze the glycemic control hemoglobin A1c (HbA1c) and LDL-C with glaucomatous damage as a microvascular complication in type 2 DM in Indonesian population.

**Materials and Methods**

This was an analytical prospective with cross-sectional study comprising 66 type 2 DM patients. Type 2 DM patients referred from Internal Medicine Department. These subjects were recruited consecutively at Universitas Sumatera Utara Hospital, North Sumatera, Indonesia, and Satellite hospital from April 2020 to August 2020 and approved by Medical Faculty University Sumatera Utara Ethics Committee. Written informed consent was obtained from all participants. The inclusion criteria in this study were type 2 DM and approved the consent form. The exclusion criteria in this study were type 2 DM patients with anterior segment infection, cataracts, and diabetic retinopathy, and use topical and oral steroid.

The primary data of patients such as age, gender, use of medications, blood pressure and duration of type 2 DM, visual acuity (VA), IOP and time of IOP measurement, visual field defect, and retinal nerve fiber layer (RNFL) thickness were documented. The participants were investigated for HbA1c and lipid profile examinations. The IOP measurement with Goldmann Applanation Tonometer Haag Streit (R900), Visual Field Defect with Octopus Perimeter (APS-T100), and RNFL analysis with spectral domain (SD) Optovue optical coherence tomography (OCT) to detect the risk of glaucomatous optic neuropathy.

**RNFL analysis**

All participants had their RNFL measured by SD Optovue OCT. The use of SD-OCT has the potential to become an important tool for assessing glaucoma progression with the sensitivity of 83% and a specificity of 88% [15].

HbA1c measurement using HbA1c kit with high performance liquid chromatography methods [16]. Based on Indonesian Association of Endocrinology classification of HbA1c level divided of two groups: HbA1c <6.5% indicate good glycemic control and HbA1c ≥6.5% indicate poor glycemic control. Diabetes was defined as HbA1c ≥6.5% and pre-diabetes was classified as HbA1c between 5.7% and 6.4% [5].

LDL-C measurement using homogeneous assay methods, according to ATP III Guidelines classification of LDL-C level divided of five groups: Optimal LDL <100 mg/dl, near optimal LDL 100–129 mg/dl, borderline high LDL 130–159 mg/dl, high LDL 160–189 mg/dl, and very high LDL >189 mg/dl [17].

**Statistical analysis**

The collected data kept in computer analyzed using Statistical Package for the Social Science version 22.0 in all participant and an analytical statistic using Chi-square test and Pearson test to analyze the correlation HbA1c level and LDL-C level with glaucomatous optic neuropathy as a microvascular complication in type 2 DM. p < 0.05 was considered significant.

**Results**

The sample of this study included 66 patients recruited from Glaucoma Department, Universitas Sumatera Utara Hospital and Satellite Hospital, Medan, Indonesia. The majority of patients are woman (71.2%), age 43–79 years old (56.42 ± 7.153), duration of type 2 DM 2–15 years (7.29 ± 4.187), VA (LogMar) 0.0–1.3 (0.58 ± 0.4347), IOP 10–30 mmHg (16.94 ± 5.239), cup-to-disc ratio (CDR) 0.3–0.9 (0.55 ± 0.148), RNFL 28.44–0.08 dB (–9.65 ± 6.411), HbA1c 5.0–13.4% (8.53 ± 2.387), lipid profile level high-density lipoprotein (HDL) 24–73 md/dl (47.75 ± 11.951), LDL 51–249 mg/dl (127.00 ± 37.307), total cholesterol 136–340 mg/dl (222.02 ± 44.619), and triglycerides 77–408 mg/dl (247.67 ± 139.986). Diagram characteristic of participant is shown in Diagram 1.

Distribution of the characteristic study subject is shown in Table 1. Correlation HbA1c level with VA, IOP, CDR, RNFL, MD, and duration of type 2 DM is shown in Table 1.
Table 2 shows the HbA1c level on VA, IOP, CDR, RNFL thickness, MD, and duration of diabetes. With Chi-square test, the p-value varies and is at p < 0.05, which means that there is a significant correlation between levels of HbA1c on VA, IOP, RNFL, MD, and duration of type 2 DM.

Correlation LDL-C level with VA, IOP, CDR, RNFL, MD, and duration of DM is shown Table 3.

Table 3 shows the LDL-C level on VA, IOP, CDR, RNFL, MD, and duration of DM. With Chi-square test, the p-value varies and is at p < 0.05, which means that there is a significant correlation between increased levels of LDL-C on VA, IOP, MD, and duration of type 2 DM.

Correlation HbA1c level and LDL-C level with VA, IOP, CDR, RNFL, MD, and duration of type 2 DM is shown in Table 4.

Table 4 shows positive and significant correlation of HbA1c level on VA (r = 0.267, p = 0.030), IOP (r = 0.259, p = 0.035), CDR (r = 0.348, p = 0.004), and duration of type 2 DM (r = 0.364, p = 0.003), while there are negative correlation HbA1c level on RNFL (r = -0.368, p = 0.0002) and MD (r = -0.264, p = 0.032). The LDL-C level shows the positive and significant correlation on VA (r = 0.244, p = 0.048), IOP (r = 0.335, p = 0.006), CDR (r = 0.253, p = 0.040), and duration of type 2 DM (r = 0.364, p = 0.042) while there are negative and not significant correlation LDL-C level on RNFL (r = -0.024, p = 0.848) and MD (r = -0.141, p = 0.376).

Discussion

In this study, the majority of these patients are female (71.2%), age range 43–79 years old with the youngest age 43 years old and the oldest age 79 years old. Prabhavati study reported that female more suffering DM cause of female more to lose protection of blood vessels due to hormonal dysfunction in which correlated with estrogen deficiency, especially after menopause and the average of DM is 41–60 years old [18]. The duration of suffering type 2 DM is 2–15 years. The study reported found the risk of metabolic syndrome in younger age with suffering of type 2 DM in longer duration [19], [20].

In this study, we found a significant correlation between levels of HbA1c on VA, IOP, CDR, RNFL, MD, and duration of type 2 DM. A study suggested that there was an increase in IOP in uncontrolled diabetics compared to those with controlled diabetes. The increase in glucose levels affects the synthesis of the excess extracellular matrix (ECM) in the trabecular meshwork cells results in the accumulation of ECM in the trabecular meshwork and causes obstruction of aqueous humor outflow. Another study found that there is a significant relationship between glaucomatous optic neuropathy and vascular disorders caused by increased HbA1c levels in patients with type 2 DM [14], [21].
We also found a significant correlation between increased levels of LDL-C on VA, IOP, MD, and duration of type 2 DM. Several studies only reported a correlation between serum lipids and the incidence of glaucomatous optic neuropathy has never been found.

The current study found the positively correlation between higher HbA1c as an indicator of glycemic control with VA (r = 0.267), IOP (r = 0.259), CDR (r = 0.348), duration of DM (r = 0.364) as a risk factor of glaucoma and negatively correlation of HbA1c on RNFL thickness (r = -0.368) and MD (r = -0.264), it means that higher HbA1c level, the RNFL getting thinner, and the visual field MD are getting worse. Evidence from another study found the positive association between glaucoma and HbA1c, suggesting that those with higher HbA1c may be have a higher risk for developing glaucoma [20], [21]. A study found that the RNFL thiner had a positive correlation with vascular disease [20], [21]. We also found the positively correlation between higher LDL-C with VA (r = 0.244), IOP (r = 0.335), CDR (r = 0.253), and duration of DM (r = 0.251) as a risk factor of glaucoma. Foster found that higher LDL-C and HbA1c correlated with higher IOP on population based from age, sex, and blood pressure [22], but the correlation between HbA1c and LDL-C with glaucomatous optic neuropathy in type 2 DM has never been found. One of the pathogenesis of glaucoma in DM patients is an increase in systemic arterial pressure which causes a decrease in optic nerve blood flow and changes the optic nerve vascular environment cause insufficient blood supply to ONH and the axons of ganglion cells. Some studies showed that diabetes will lead to excessive fibronectin accumulation in the trabecular meshwork increased aqueous outflow.

An increase in blood sugar levels can trigger an osmotic gradient so that fluids will shift to the intraocular space resulting in an increase in IOP [23], [24]. Glucose interacts with free amino acid protein residues and ages can be deposited on the collagen artery walls and cause pathological cross-linking. Age-mediated cross links have high resistance to enzymatic proteolysis and low degradation rates, which may contribute to increased collagen content in arterial walls, characteristic in aging and accelerated in DM [25].

A in vivo study showed that both increased IOP and visual field defects were significantly correlated with the degree of oxidative DNA damage. The relationship between oxidative stress and glaucoma to LDL/HDL has been a concern in various studies because of its antioxidant effects throughout the body [26].

Conclusion

Our findings reveal that subjects with higher HbA1c and LDL-C have correlation with higher IOP, thinner RNFL, loss of visual field defect MD as a risk factor of glaucomatous damage and correlated with duration of disease in type 2 DM. In the light of our findings and the evidence from the previous report, HbA1c as an indicator of glycemic control in DM correlated with glaucomatous optic neuropathy.

Advantage of research is that glycemic control and LDL-C with glaucomatous optic neuropathy

Table 3: Correlation LDL-C level with VA, IOP, CDR, RNFL, perimetry MD, and duration of DM type 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>LDL-C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA &lt;0.2–0.1</td>
<td>0.006*</td>
<td>0.047*</td>
</tr>
<tr>
<td>VA 0.2–0.5</td>
<td>0.01</td>
<td>0.048*</td>
</tr>
<tr>
<td>VA 0.6–0.9</td>
<td>0.259</td>
<td>0.040*</td>
</tr>
<tr>
<td>VA ≥1.0</td>
<td>0.040*</td>
<td>0.000*</td>
</tr>
<tr>
<td>IOP ≤21 mmHg (normal)</td>
<td>13 (27.1)</td>
<td>0.040*</td>
</tr>
<tr>
<td>IOP &gt;21 mmHg (high)</td>
<td>3 (16.7)</td>
<td>0.000*</td>
</tr>
<tr>
<td>CDR Normal: 0.2–0.3</td>
<td>1 (25.0)</td>
<td>0.335</td>
</tr>
<tr>
<td>CDR Mild: 0.3–0.5</td>
<td>12 (31.6)</td>
<td>0.040*</td>
</tr>
<tr>
<td>CDR Moderate: 0.6–0.7</td>
<td>3 (15.8)</td>
<td>0.040*</td>
</tr>
<tr>
<td>CDR Severe: 0.8–1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RNFL Normal: &gt;80nm</td>
<td>6 (27.3)</td>
<td>0.000*</td>
</tr>
<tr>
<td>RNFL Borderline: 70–79nm</td>
<td>2 (10.0)</td>
<td>0.348</td>
</tr>
<tr>
<td>RNFL Outside normal: &lt;60nm</td>
<td>8 (33.3)</td>
<td>0.000*</td>
</tr>
<tr>
<td>MD Perimetry Mild: &gt;4–6dB</td>
<td>9 (31.0)</td>
<td>0.040*</td>
</tr>
<tr>
<td>MD Perimetry Borderline: 12 &lt; MD &lt;=18</td>
<td>1</td>
<td>0.000*</td>
</tr>
<tr>
<td>MD Severe: &lt;=12dB</td>
<td>6 (24.0)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Duration of DM DM ≤5 years</td>
<td>5 (22.7)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Duration of DM DM 6–10 years</td>
<td>11 (33.3)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Duration of DM DM &gt; 10 years</td>
<td>3 (27.3)</td>
<td>0.034*</td>
</tr>
</tbody>
</table>

Table 4: Correlation HbA1c level and LDL-C level with VA, IOP, CDR, RNFL Perimetry MD, and duration of DM type 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>HbA1c</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>VA</td>
<td>IOP</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>VA</td>
<td>0.267 (0.030*)</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>p</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

Chi-square test, significant < 0.05, VA: Visual acuity, IOP: Intraocular pressure, CDR: Cup-to-disc ratio, RNFL: Retinal nerve fiber layer, MD: Mean deviation, DM: Diabetes mellitus.
as a microvascular complication in type 2 DM is still rarely studied. The limitation of this study, it was not population based but rather health center based, may cause a selection bias but further studies are needed to prospective longitudinal clinical trials on larger populations and longer more times to conclude another the risk factor and marker which correlated with quality of life in glaucoma.

References


