

Correlation of Retinal Nerve Fibre Layer Thickness with HbA_{1c} and Oxidised LDL in Non-proliferative Diabetic Retinopathy

Yusof Nor-Sharina^{1,2}, Embong Zunaina^{1,2*}, Ismail Shatriah^{1,2}, Kyi Win-Mar^{2,3} and Ab-Rahman Azriani^{2,4}

¹Department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia, Malaysia

²Hospital Universiti Sains Malaysia, Malaysia

³Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia, Malaysia

⁴Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, Malaysia

Abstract

Objectives: The purpose of this study is to determine the correlation of retinal nerve fibre layer (RNFL) thickness with glycosylated haemoglobin (HbA_{1c}) and oxidised low density lipoprotein (LDL) among Type 2 non-proliferative diabetic retinopathy (NPDR).

Methodology: This is a cross-sectional study involving 125 patients with Type 2 NPDR (mild NPDR: 45 patients, moderate NPDR: 45 patients and severe NPDR: 35 patients). Patients were evaluated for peri-papillary RNFL thickness by Heidelberg Retina Tomography. Blood were taken for HbA_{1c} and oxidised LDL.

Results: Severe NPDR showed the highest mean RNFL thickness (severe: 762.60 SD 209.57 µm, moderate: 738.24 SD 200.30 µm, mild: 700.27 SD 215.44 µm), however it was not significant (p=0.40). There was significant fair negative correlation between RNFL thickness and oxidised LDL in NPDR (r= -0.391, p<0.001). However, there was no significant correlation between RNFL thickness and HbA_{1c} (r=0.048, p=0.60).

Conclusion: Early NPDR appears to have thinner RNFL thickness and is significantly correlated with high level of oxidised LDL.

Keywords: Diabetes; Retinal nerve fibre layer; Oxidised LDL; Glycosylated haemoglobin

Abbreviation: RNFL: Retinal Nerve Fibre Layer; HbA_{1c}: Glycosylated Haemoglobin; LDL: Low Density Lipoprotein; NPDR: Non-Proliferative Diabetic Retinopathy; HRT: Heidelberg Retina Tomograph; OCT: Optical Coherence Tomography; ELISA: Enzyme-Linked Immunosorbent Assay; Hb-AGE: Haemoglobin Advanced Glycation End-Products; ApoB: Apolipoprotein B

Introduction

Normal vision depends on the normal function of the retinal neurons to produce a good quality of vision. The quality of vision starts to deteriorate early in diabetes, before the clinical retinopathy becomes evident, probably indicating the early signs of neuronal dysfunction.

Retinal nerve fibre layer (RNFL) is an important structural neuron in the retina layer which is often shown to affect in the early pathogenesis of diabetic retinopathy. Several studies have reported RNFL thinning or defects in people with diabetes [1-5]. Histological studies of neural components of the retina have revealed that diabetes-induced biochemical mechanisms can potentially cause neural cell degeneration [6,7]. An in-depth understanding of the vascular changes in the retina during diabetes has given cause for the treatment of diabetic retinopathy. Indeed, the only proven treatment for diabetic retinopathy apart from intensive insulin therapy is laser photocoagulation, which involves the destruction of the retinal regions which contains overt vascular abnormalities [8]. Subsequently, early detection of RNFL thinning may help ophthalmologists to provide effective treatment of diabetic retinopathy and with early prevention, thus reducing vision loss.

Nowadays, due to the new introduction of imaging devices such as Heidelberg Retina Tomograph (HRT) and optical coherence tomography (OCT), RNFL thickness can be measured quantitatively

and evaluated in vivo. The advantages of high reproducibility and low interobserver and interobserver variability as well as easy handling have increased these popular diagnostic tools.

With regards to pathogenesis of diabetic retinopathy, the development and progression of diabetic complications are related strongly to the degree of glycemic control and hyperlipidaemia. Recently, glycosylated haemoglobin (HbA_{1c}) measurement is regarded as the gold standard indicator for glycemic control in diabetic patients, reflecting glucose levels over a 2-3 months period [9,10].

Oxidised low density lipoprotein (LDL) derived from LDL-cholesterol under oxidative stress, encompasses many atherogenic properties [11]. Oxidised LDL is an independent predictor of endothelial dysfunction with pro-inflammatory, pro-thrombotic and pro-apoptotic properties in individuals suffering from oxidative stress such as diabetic patients [12,13].

Guidelines for the management of the lipid profile in diabetic patients are mainly focused on controlling LDL cholesterol, triglycerides, high density lipoprotein-cholesterol and total cholesterol [14]. To date, there is still a lack of data concerning the role of atherogenic lipids such as

*Corresponding author: Embong Zunaina, Department of Ophthalmology, School of Medical Sciences, Universiti Sains, Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia, Tel: 609 767 6362; Fax: 609 765 3370; E-mail: zunaina@kb.usm.my

Received July 31, 2013; Accepted September 16, 2013; Published September 21, 2013

Citation: Nor-Sharina Y, Zunaina E, Shatriah I, Win-Mar K, Azriani AR (2013) Correlation of Retinal Nerve Fibre Layer Thickness with HbA_{1c} and Oxidised LDL in Non-proliferative Diabetic Retinopathy. J Diabetes Metab 4: 298. doi:10.4172/2155-6156.1000298

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oxidised LDL levels among diabetic patients with retinopathy, whether there is a significant correlation between oxidised LDL with the retinal nerve fiber layer.

Our aim of this study is to determine the RNFL thickness in non-proliferative diabetic retinopathy (NPDR) and to evaluate the correlation of RNFL thickness with HbA_{1c} and oxidised LDL.

Methods

Participants

This study is a cross-sectional study and deals with NPDR among Type 2 diabetes mellitus. One hundred and twenty five patients with NPDR attending to Eye Clinic, Hospital Universiti Sains Malaysia, Kelantan from January 2010 to December 2011 were recruited in the study. Informed consent was obtained for every patient including a detailed explanation of all the procedures.

Patients were selected based on the following criteria: (i) Type 2 Diabetes mellitus with NPDR, (ii) Age between 40-65 years old, (iii) Duration of diabetes more than 5 years, and (iv) Clear view of the retina with minimal cataract. Eyes with high myopia, optic neuropathy, advanced cataract and cloudy media were excluded from the study. We also excluded a case of diabetic retinopathy with previous history of laser, previous history of vitreoretinal surgery, diabetic retinopathy with extensive diabetic macular oedema extending to peri-papillary region and other retinopathy due to hypertension or vascular disease.

Study procedure

The demographic data was taken from the patients or from the medical records. Then, the patient underwent fundus examination, retinal nerve fibre layer thickness measurements and blood test for measurement of HbA_{1c} and oxidised LDL. The pupils were dilated by topical dilating drops using 1% tropicamide and phenylephrine 2.5% for fundus examination. Examination of fundus was performed using +90Diopter with a slit lamp bio microscopy. Then, fundus photograph was taken for grading of non-proliferative diabetic retinopathy based on proposed International Diabetic Retinopathy Severity Scales [15]. Only one eye was selected for one patient in view that the systemic outcomes were similar for both eyes. If the two eyes had unequal distribution of diabetic retinopathy, the more affected eye was selected. If the patient has one eye with hazy media and the other eye with clear media, the eye with clear media was selected.

After the study eye has been chosen, the subject underwent the RNFL thickness measurement using HRT III (Heidelberg Engineering, Heidelberg, Germany). During the procedure, the subject needs to relax with forehead rested on the headrest during the camera focusing the image. The procedure was performed by a trained medical operator. After the good image has been obtained, the operator will draw the contour line along the inner sclera ring of the optic nerve. The contour line was drawn manually by the same operator. Then, the image were analysed using the standard reference plane. The RNFL thickness and cross-sectional area were calculated in the image analysis.

After the RNFL thickness measurement has been done, patient was informed to come fasting during the next visit (within one week) for blood test (HbA_{1c} and oxidised LDL). Five ml of fasting venous blood was taken; three ml was collected for HbA_{1c} while another two ml of blood was collected for oxidised LDL analysis. The oxidised LDL was measured by sandwich enzyme-linked immunosorbent assay (ELISA) using commercial kit (ALPCO Immunoassay). All steps were followed according to the manufacturer's instruction. The absorbance

is determined immediately with an ELISA reader at 450nm. The intra-assay and inter-assay coefficient of variation for the assay ranged between 3.9% and 11.0%. The percentage of the A1c component of HbA_{1c} was assessed by high performance liquid chromatography. The HbA_{1c} references range in our laboratory was 4.5% to 6.5 % [16].

Ethical approval

The study was approved by the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia {Ref: USMKK/PPP/JEPeM [222.3.(14)]}.

Statistical analysis

Data were analysed using SPSS version 18.0. Descriptive analyses were used for the mean values and SD. All values were tested for normal distribution and equal variances in three groups. For demographic data, One-way Anova test was used for comparison of three groups of mean (age and gender distribution) whereas Fisher Exact test was used for comparison of categorical data (ethnicity). The mean RNFL thickness and HbA_{1c} were tested by comparison of three means using One-way Anova test for parametric test whereas Kruskal-Wallis was used to compare Oxidised LDL for non-parametric test. Mann Whitney test was used for non-parametric Independent t test. P value <0.05 was taken as significant data. The correlation between RNFL thickness with HbA_{1c} was tested using Pearson correlation for bivariate normal distribution data whereas the correlation between RNFL thickness with oxidised LDL was tested using Spearman correlation for non-parametric test. The correlation coefficient, *r* is grading as below [17]:

- 0 : no correlation
- < 0.25 : poor
- 0.26 - 0.50 : fair
- 0.51 - 0.75 : good
- 0.76 - 1.0 : excellent
- +1 : perfect positive relationship
- -1 : perfect negative relationship

Results

Demographic data

A total of 125 patients were recruited in the study. There were divided into three groups; mild NPDR (45 patients), moderate NPDR (45 patients) and severe NPDR (35 patients). There was no statistically significant difference in mean age between mild NPDR (56.91, SD 5.34), moderate NPDR (55.31, SD 5.11) and severe NPDR (56.09, SD 5.27) (*p*=0.35). There was also no statistically significant difference in gender (*p*=0.23) and ethnic group (*p*=0.26) among the three groups of NPDR (Table 1).

Most of our study population were Malays whom represented 92% whereas another 8% were from non-Malay ethnics; Chinese and Indian. This numbers reflects the normal racial population in Kelantan, Malaysia where Malay is the dominant population in Kelantan. The percentage of male and female gender was almost equally distributed among NPDR groups. There was no significant difference in gender distribution among the three groups of NPDR.

Retinal nerve fibre layer, HbA_{1c} and oxidised LDL

The mean RNFL thickness in all groups of NPDR was 731.39 μ m

Variable	Mild NPDR n= 45	Moderate NPDR n=45	Severe NPDR n=35	p value
Age (year) (Mean, SD)	56.91 (5.34)	55.31 (5.11)	56.09 (5.27)	0.35 ^a
Gender (n, %)				
Male	24 (30.9)	24 (35.3)	19 (33.8)	0.23 ^a
Female	21 (42.1)	21 (36.8)	16 (21.1)	
Ethnic (n, %)				
Malay	39 (33.9)	42 (36.5)	34 (29.6)	0.26 ^b
Chinese	5 (62.5)	3 (37.5)	0	
Indian	1 (50.0)	0	1 (50.0)	
RNFL thickness (µm) (Mean/ SD)	700.27 (215.44)	738.24 (200.30)	762.60 (209.57)	0.40 ^a
HbA _{1c} (Mean/SD)	9.57 (2.17)	9.87 (2.16)	10.41 (2.78)	0.29 ^a
Oxidised LDL (Median/IQR)	297.40 (766.20)	259.74 (731.40)	90.18 (325.50)	0.03 ^c

^aOne –way Anova test, ^bFisher exact test, ^cKruskal-Wallis test, p value < 0.05 (significant)

Table 1: Distribution of age, gender, ethnic group, mean RNFL thickness, HbA_{1c} and Oxidised LDL level in NPDR.

Quadrant RNFL thickness (µm)	Mild NPDR (Mean/SD)	Moderate NPDR (Mean/SD)	Severe NPDR (Mean/SD)	F(df)	p value
Superior	619.64 (236.28)	685.33 (274.05)	687.69 (238.96)	1.016 (2/124)	0.36
Temporal	624.82 (217.78)	618.62 (195.14)	692.31 (221.49)	1.420 (2/124)	0.25
Nasal	931.47 (369.74)	951.22 (318.41)	1011.23 (287.65)	0.606 (2/124)	0.55
Inferior	653.24 (233.68)	651.38 (272.71)	693.69 (351.83)	0.267 (2/124)	0.77

One-way Anova test, p value < 0.05 (significant)

Table 2: Comparison of mean RNFL thickness based on quadrants in NPDR.

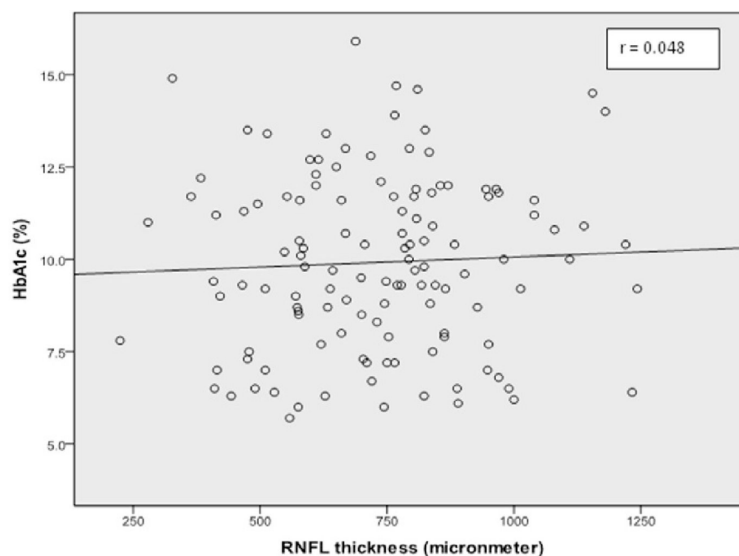


Figure 1: Correlation between RNFL thickness with HbA_{1c} in all groups of NPDR.

(SD 208.31) (range of RNFL thickness between 300 µm–1280 µm). Table 1 shows the distribution of mean RNFL, HbA_{1c} and oxidised LDL in three groups of NPDR. Severe NPDR showed the highest mean RNFL thickness among the three groups of NPDR. However, there was no significant difference in the mean RNFL thickness among the three groups of NPDR (p=0.40). Based on subgroup quadrant of RNFL thickness, there was no significant difference in the mean RNFL thickness among the three groups of NPDR in all quadrants (p value between 0.25 and 0.77) (Table 2). The level of mean HbA_{1c} was highest in severe NPDR. However, there was no significant difference in mean HbA_{1c} among the three groups of NPDR (p=0.29). The highest level of oxidised LDL was observed in mild NPDR and the lowest level was in severe NPDR group. There was significant difference of oxidised LDL

between mild, moderate and severe NPDR (p=0.03). Further analysis of oxidised LDL with Mann Whitney test, there was a significant difference between mild and severe NPDR (p=0.02) and also between moderate and severe NPDR (p=0.02).

Correlation between RNFL thickness with HbA_{1c}

Figure 1 shows the correlation between RNFL thickness with HbA_{1c} in all groups of NPDR. There was poor positive correlation (r=0.048, p=0.60) between HbA_{1c} and RNFL thickness (Table 3).

Correlation between RNFL thickness with Oxidised LDL

Figure 2 shows the correlation between RNFL thickness with

	r	p value
RNFL thickness with HbA _{1c}		
All groups of NPDR	0.048	0.60 ^a
RNFL thickness with Oxidised LDL		
All groups of NPDR	-0.391	< 0.001 ^b
Mild NPDR	-0.598	< 0.001 ^b
Moderate NPDR	-0.268	0.07 ^b
Severe NPDR	-0.199	0.25 ^b

^aPearson correlation, ^bSpearman correlation, p value < 0.05(significant)

Table 3: Correlation of RNFL thickness with HbA_{1c} and Oxidised LDL in NPDR.

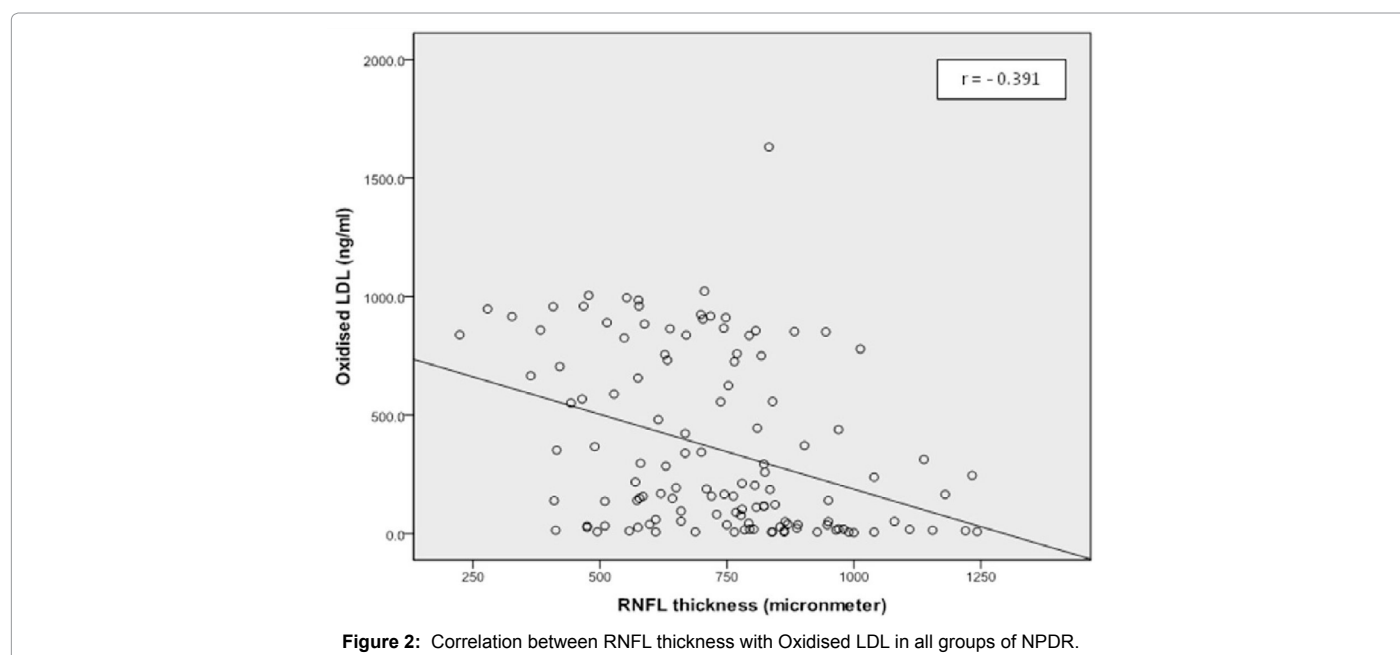


Figure 2: Correlation between RNFL thickness with Oxidised LDL in all groups of NPDR.

oxidised LDL in all groups of NPDR. There was significant fair negative correlation ($r=-0.391$, $p<0.001$) between RNFL thickness and oxidised LDL in all groups of NPDR. Among the three groups of NPDR, only mild NPDR showed significant good negative correlation ($r=-0.598$, $p<0.001$) between RNFL thickness and oxidised LDL (Table 3).

Discussion

From our findings comparing the mean RNFL thickness based on quadrant in each groups of NPDR, we did not discover any significant difference in regards to the mean RNFL thickness among three groups of NPDR. However, among each quadrant, nasal quadrant is the thickest part in all NPDR. We also observed the superior and temporal quadrants were thinner compared to other quadrants. Our results were fairly similar to studies done by Lopes de Faria et al. [2] and Takahashi et al. [3], which disclosed that RNFL was thinner in the superior quadrant. This finding corroborates with previous study by Kern [18] showing that the early events of diabetic retinal disease (micro aneurysms and acellular capillaries) occur preferentially in the superior temporal quadrant rather than in inferior areas [18].

Among other studies, Chung et al. demonstrated that blood flow in the superior temporal retina increased in response to hypercapnia, but did not decrease in response to hyperoxia. In contrast, hyperoxia led to a decrease in blood flow to the inferior retina, whereas hypercapnia did not result in an increased blood flow within this area [19]. The lack of normal vasoconstrictor response in this superior quadrant could

explain why this region is more susceptible to micro aneurysms and acellular capillaries in diabetes mellitus and also why the retinal fibres are preferentially lost in this region even before clinically detectable diabetic retinopathy [18]. Sugimoto postulated that the superior quadrant was more susceptible to undergoing damage compared with other areas and may have a tendency for higher rates of cell death, which results in RNFL thinning [20]. Besides this, we also noticed that the thickest RNFL in nasal quadrant might be due to the lack of micro aneurysm presence in this area and therefore less retinal nerve fibre layer damage occurred in this quadrant.

Several studies have been reported on RNFL thinning, defects or both in diabetes mellitus [1,2,21,22]. In our study, we measured the RNFL thickness in three groups of NPDR and compared the mean RNFL thickness in each groups of NPDR. We found that there were no significant differences in mean RNFL thickness among the three groups of NPDR; however, we observed that the mean RNFL thickness was higher in severe NPDR. Our findings were in parallel to other studies done by Takahashi et al. [23] and Tekeli et al. [24]. In study done by Tekeli et al. [24], HRT was used to evaluate optic nerve head parameter in diabetes mellitus with and without retinopathy. Whereas, Takahashi et al. [23] used the stratus OCT which is a different tool compared with our study. Both studies did not find any significant reduction in the RNFL thickness among subjects of mild to moderate NPDR compared with age-matched healthy subjects. Based on findings found by Takahashi et al. [23], we were able to make an assumptions that, the possibilities of increased RNFL thickness in severe NPDR may be due

to effects from hard exudates and retinal haemorrhages from leaking blood vessels causing the accumulation of intra-retinal fluids which subsequently cause the retina to become oedematous and contributes to an increased thickness of the retinal nerve fibre layer. Although, we have excluded the patients with clinically apparent and extensive retinal oedema, a possible subclinical retinal oedema still presents itself in our diabetic patients; this finding may interfere with measurements effected by HRT.

HbA_{1c} is known as an index of mean blood glucose in fasting and the postprandial state [25], and is well established and widely used as a clinical measure of chronic glycaemia [26]. HbA_{1c} of 6.5% has not been seen as sufficiently sensitive and specific to identify individuals who are at risk of developing diabetic retinopathy [27]. From our findings, we noted that the majority of our subjects in NPDR groups had poor glycemic control. The majority of them had HbA_{1c} \geq 6.5%. The mean HbA_{1c} in mild NPDR was 9.571 (2.17) which is not vitally different from moderate NPDR 9.876 (2.16) and severe NPDR 10.411 (2.78). Our results of mean HbA_{1c} were consistent with other studies [19,21,28].

We did not find any momentous correlation between RNFL thickness with the HbA_{1c} in NPDR groups. Our findings were supported by other studies [1,21,24,29]. Study conducted by Ozdek et al. [21] compared diabetic patients whose blood glucose was well regulated and with those who were not well regulated according to the levels of blood glucose, HbA_{1c}, fructosamine and triglyceride. They found that the average RNFL thickness value obtained by scanning laser polarimetry was reduced in patients without diabetic retinopathy who had poor blood glucose control but not for those with good control. However, the level of HbA_{1c} showed no significant relation with the reduction of RNFL either in our study or other studies reported by Chihara et al. and Peng et al. [1,29].

Although, the HbA_{1c} level has been recognised as an index of glucose control within the period of 3 months, however haemoglobin advanced glycation end-products (Hb-AGE) might be better than HbA_{1c} as a long-term predictor because of its stability [30]. Hb-AGE concentration in blood appears to reflect glucose control over a longer period of the red cell life than the slowly reversible HbA_{1c}. Hence, Hb-AGE measurements were proven as a superior clinical index of long-term glycemic control [30]. This might explain why there was no correlation between a single test of HbA_{1c} and RNFL thickness as seen in our study and other studies [1,29]. The level of HbA_{1c} at the time of examination was not correlated to the incidence of nerve fibre loss which was explained by Chihara et al. [1]. These discrepancies are due to fluctuation in the HbA_{1c} level as well as the level of glycemic control at the time of examination and do not reflect the severity of diabetic retinopathy [1]. Apart from HbA_{1c}, fasting blood sugar and post-meal blood sugar also act as equivalent predictors for retinopathy [31].

With regards to pathogenesis, dyslipidaemia has been associated with the severity of diabetic retinopathy in clinical studies [32,33]. Specifically, diabetic retinopathy was positively associated with serum triglycerides, serum concentration LDL, LDL particle concentration and apolipoprotein B (ApoB), the principal lipoprotein component of LDL [32]. Oxidised LDL derived from LDL-cholesterol under oxidative stress; encompass many atherogenic properties [11] which have been implicated in the progression of diabetic retinopathy [34].

In our study based on oxidised LDL among NPDR, we noticed a significant disparity in the median of oxidised LDL among three groups of NPDR. The level of oxidised LDL was higher in mild NPDR, and

followed by moderate NPDR. The level of oxidised LDL was noticeably lower in severe NPDR. The repeated Mann Whitney revealed the significant differences seen between mild-severe NPDR and moderate-severe NPDR.

From our study, we found a significant fair negative correlation ($r=-0.391$, $p<0.001$) between RNFL thickness with oxidised LDL in NPDR. Among all types of NPDR, mild NPDR showed a significantly good negative correlation ($r=-0.598$, $p<0.001$) between RNFL thickness and oxidised LDL. However, there was borderline fair negative correlation seen between RNFL thickness and oxidised LDL in moderate NPDR whereas poor negative correlation seen in severe NPDR group.

We report a significant association of oxidised LDL with RNFL thickness in NPDR especially in mild NPDR. It was reported that serum oxidised LDL levels are considerably higher in diabetic patients than in healthy individuals [11,13,35]. In a study done by Wu et al. [34], they presented important pieces of evidence to support a role of extravasated and modified lipoproteins, specifically oxidised and glycated LDL, in the etiology of pericytes loss in the early stages of diabetic retinopathy. First, they demonstrated the presence of extravagated and oxidised LDL in the diabetic retina using antibodies raised against copper-oxidised LDL. The extent of staining for ApoB and oxidised LDL were proportional to the severity of retinopathy. Wu et al. [34], also found at the earliest stages, before clinical diabetic retinopathy was evident, that the aggregation of lipoproteins was observed. Secondly, Wu et al. [34] also observed that oxidised LDL was expressed throughout all layers of the retina, mainly in the ganglion cell layer adjacent to retinal blood vessels in NPDR. The injurious effects of oxidised LDL are likely to affect the neural retina and the retinal blood vessels, consistent with recent concepts of a general retinal injury in diabetic retinopathy [36,37]. Fu et al. suggest that oxidative stress and endoplasmic reticulum stress are induced by modified LDL, and are implicated in pericyte loss in diabetic retinopathy [38]. Diabetes is a progressive inflammatory condition. As the disease becomes prolonged, elevated free radical formation, elevated inflammatory cytokines and an overwhelming endogenous anti-inflammatory response, propagate the oxidative stress in diabetic patients [39,40]. These findings have verified our study results in which possibilities of RNFL is threatened by oxidised LDL at an early stage of retinopathy.

Conclusion

Early NPDR appears to have thinner RNFL thickness and is significantly correlated with high level of oxidised LDL. A large population cohort study is needed to establish the correlation between oxidised LDL and RNFL thickness in the management of lipids in diabetic patients.

Acknowledgement

This study was supported by a Research University Grant (1001/PPSP/812064) from Universiti Sains Malaysia.

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Citation: Nor-Sharina Y, Zunaina E, Shatriah I, Win-Mar K, Azriani AR (2013) Correlation of Retinal Nerve Fibre Layer Thickness with HbA_{1c} and Oxidised LDL in Non-proliferative Diabetic Retinopathy. *J Diabetes Metab* 4: 298. doi:10.4172/2155-6156.1000298