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Review Article

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Association of Glucose Levels with Peripapillary Retinal Nerve Fiber Layer Thickness in Non-Proliferative Diabetic Retinopathy

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Abstract

Purpose: *To assess whether degree of glycosylated hemoglobin levels influence peripapillary retinal nerve fiber layer thickness in patients with non-proliferative diabetic retinopathy.*

Methods: *A prospective observational cross section study was performed on 110 eyes included 30 eyes of 15 healthy control subjects and 80 eyes of 40 patients with non-proliferative diabetic retinopathy. Diabetic group was divided into two study groups, subgroup 1 with HbA1c that is less than 7% and subgroup 2 with HbA1c that is equal or more than 7%. Full ophthalmic examinations included best-corrected visual acuity, anterior segment evaluation, and intraocular pressure assessment. Peripapillary retinal nerve fiber layer thickness (RNFLT) was measured using a spectral-domain OCT (Topcon Corporation, Tokyo, Japan). Multivariable logistic regression models were used after controlling for the same sets of confounders. A value of $P < 0.05$ was considered significant.*

Results: *There was non-statistically significant difference regarding systemic hypertension, BCVA, intraocular pressure, while, there was statistically significant difference regarding smoking, body mass index, HBA1C, lipid profile between diabetic and control groups. There was statistically significant decrease in peripapillary RNFLT in superior quadrants in diabetics group with impairment of HBA1C ($P<0.001$). Peripapillary RNFLT was negatively correlated with HbA1c in the supe¬rior, inferior, and nasal quadrants, while it was positively correlated in the temporal quadrant*

Conclusion: *Impairment of glycemic control affects the peripapillary RNFLT mainly in the superior quadrant. The measurement of peripapillary RNFLT may become a useful method to monitor early retinal changes in diabetic patients.*

Keywords: Glucose Level, Peripapillary, RNFL, Diabetics

1. Introduction

Diabetes mellitus is considered one of the most epidemic diseases of the 21st century, showing a high prevalence of 2%–6% worldwide [1]. It is a multifactorial metabolic disease clinically presenting as sustained hyperglycemia together with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [2]. The World Health Organization defined DM as a fasting venous plasma glucose level that is equal to or higher than 7.0 mmol/L or venous plasma level is equal to or greater than 11.1 mmol/L, measured 2 hours after oral intake of 75 g glucose [4].

Diabetes mellitus (DM) is one of the most common endocrine disorders affecting more than 400 million people worldwide [4].

Chronic hyperglycemia is well known to cause activation of several pathological molecular pathways involved in the pathogenesis of various DM complications which may involve almost every tissue in the human body [5,6].

Diabetic retinopathy (DR) is the most common complication of this chronic disorder [7]. DR clinically presents as retinal ischemia, intraretinal microvascular abnormalities, hemorrhages, neovascularization, and increased vascular permeability [8]. It can progress from mild, non-proliferative to moderate or severe non-proliferative disease, which may consequently result in proliferative disease [9].

Glycosylated hemoglobin (HbA1c) was recommended as an excellent predictive marker for the diagnosis of diabetes [10]. Each 1% reduction in HbA1c minimizes the risk of developing systemic and ocular com¬plications by 40%. The measurement of HbA1c is consid¬ered as important as blood glucose measurement. HbA1c is a reflection of average plasma glucose over the past 2–3 months and does not require patients to fast and can be measured at any time. Recently, there has been an increased interest to use HbA1c as a marker for screening of those at high risk of developing diabetes as it shows high sensitivity and specificity [11].

The use of HbA1c is considered as one of the most dis¬criminative and effective tools for the diagnosis of diabetic patients who are vulnerable to develop complications including retinopathy [12]. An association between HbA1c and mortality risk factors among men and women with type 2 diabetes was reported [13].

Retinal neuro-degeneration has been suggested as a cause of early diabetic retinal damage, supported by evidence from different electrophysiological and experimental studies showing neuronal apoptosis, ganglion cell loss, glial reactivity, and selective thinning of retinal inner layers. Such changes may occur before the onset of microvascular changes and can be considered as an early marker of DR [14,17].

Optical coherence tomography (OCT) is a noninvasive imaging modality with a fast acquisition time. It provides in vivo high-resolution three-dimensional images of the retinal layers and allows thickness assessment of the whole retina as well as individual retinal layers in comparison to normative database [18].

The current study was achieved to assess correlation between controlled HbA1c and uncontrolled HbA1c on peripapillary retinal nerve fiber layer thickness (RNFLT) in diabetic patients as marker of severity of retinopathy. The obtained data might support the suggestion of the use of the noninvasive role as a protective strategy against retinopathy, a complication of DM that may consequently lead to blindness.

2. Patients and Methods

This was prospective observational cross section study conducted from January 2024 till October 2024. All participants signed an informed consent before study contribution. The 1964 Declaration of Helsinki and its later amendments or equivalent ethical standards were followed during study.

2.1. Patients

The study included 80 eyes of 40 patients with non-proliferative diabetic retinopathy (NPD) and 30 eyes of 15 healthy control subjects attending AL-Noor eye laser center in Mansoura. Inclusion criteria for diabetic cases included documented diagnosis of type 2 DM (fasting glucose above 120mg/ml or postprandial glucose >150mg/ml and under treatment), age between 40-75 years, and no clinical or angiographic changes of diabetic retinopathy. For healthy non-diabetic control subjects with normal glucose levels in previous 6 months, age between 40-75 years were included in the study.

Any history of glaucoma, steroid medication topical/oral, corneal opacity, and central corneal thickness above 600 microns or below 450 microns were excluded. Errors of refraction (spherical equivalent >±3 diopters) or media opacity preventing acquisition of good quality OCT images were also considered as exclusion criteria. Any retinal pathology not associated with diabetes mellitus such as retinal arteriolar alterations, exudates, cotton wool spots, hemorrhage, extensive micro-vascular abnormalities and papilledema in hypertensive retinopathy were excluded. Neurodegenerative diseases known to affect RNFL as Parkinson's disease, trauma or intraocular surgery were excluded.

All participants were asked about their socio-demographics, lifestyle factors (e.g., smoking status), medical history (e.g., history of diabetes or hypertension), ocular history (i.e., cataract surgery and refractive surgery), and medications. The health examination included anthropometry, blood pressure, laboratory measurements, and ocular examinations.

Anthropometric parameters, including weight, and height, were measured. The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was taken twice in the sitting position, and the mean value of these two successive readings was recorded. Blood samples were collected for measurements of serum glucose (fasting or non-fasting), HbA1c, cholesterol, HDL, LDL and triglyceride concentrations.

All participants underwent a full ophthalmological examinations including best-corrected visual acuity (BCVA) assessment using Landolts broken ring chart then converted to Log MAR, slit-lamp biomicroscopy for anterior segment evaluation, intraocular pressure measurement using Goldmann applanation tonometer, gonioscopy with three-mirror lens, dilated funduscopic examination with Volk 90 D and fundus fluorescin angiography (Heidelberg Engineering GmbH, Heidelberg, Germany), and CCT was measured using a ultrasound pachymeter (DGH, Exton, PA, USA).

Diabetic retinopathy is classified according to grades of severity as per International clinical diabetic retinopathy severity scale [19]. No apparent signs show no diabetic retinopathy. Mild to moderate non-proliferative diabetic retinopathy (NPDR) characterized with

micro-aneurysms, retinal hemorrhages, exudates, cotton wool spots, venous beading and intraretinal microvascular aneurysms.

Participants were divided into 30 healthy controls eyes including healthy participants with fasting plasma glucose less than 7 mmol/liters and/or HBA1c less than 6%. Diabetic group subdivided into subgroup 1; 46 eyes (controlled diabetics) including participants with type 2 DM and HBA1c less than 7% and subgroup 2; 34 eyes (uncontrolled diabetics) including participants with type 2 DM and HBA1c greater than or equal to 7%.

3. Glycosylated Hemogloblin Assessment

Assessment of glycemic control was performed using A1cNow+ system, which provides quantitative measurement of HbA1c level in a capillary or venous blood sample [19]. Glycated hemoglobin (HbA1c) is a blood test, which doesn't require not eating for a period of time (fasting), shows average blood sugar level for the past 2 to 3 months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. The higher blood glucose levels, the more hemoglobin with sugar attached. An HbA1c level of 7 % or higher on two separate tests means that have diabetes. An HbA1c between 5.7% and 6.9% means that have pre-diabetes. Below 5.7% is considered normal.

Random blood sugar test, a blood sample will be taken at a random time. No matter when you last ate, a blood sugar level of 200 milligrams per deciliter (mg/dL) 11.1 millimoles per liter (mmol/L) or higher suggests diabetes. Fasting blood glucose test, a blood sample will be taken after haven't eaten anything the night before (fast). A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered pre-diabetes. If it's 120 mg/dL (7 mmol/L) or higher on two separate tests, or postprandial glucose >150mg/ml suggests diabetes.

3.1. RNFL Assessment

Optical coherence tomography (OCT) is a novel, noninvasive, three-dimensional imaging technique that allows for the visualization of retinal nerve fiber layers. Peripapillary RNFL parameters were obtained using spectral domain OCT device (Topcon Corporation, Tokyo, Japan). Peripapillary RNFL thickness is measured between the inner plexiform layers and the nerve fiber layer along a circle of 3.45mm diameter centered at the optic nerve head.

Prior to OCT examination, mydriatic eye drops were administered to dilate the pupils as much as possible in order to ensure the best possible OCT signal and analysis in the patients' eyes. The chin rest was placed over the patient's chin. The patient was instructed to focus on a certain place inside the device. A camera that shows the fundus and scan beam is housed inside the device to complete this step. Optic disc map for peripapillary RNFL thickness; a 6.0 x 6.0 mm area centered on the optic disc was covered using a 3D raster scan protocol with 512 A-scans and 256 B-scans (6.0 x 6.0 mm - 512 x 256).

To center the scanning area, the patient was instructed to fixate on an internal fixation light (SMART Track). Prior to obtaining an OCT image, the OCT signal location and signal quality were automatically improved by machine learning. The software used motion control techniques to eliminate saccades and slight fixation loss once the volumetric OCT dataset was finished. After discarding low-quality scans, the process was repeated until high-quality scans were obtained. A mean of three measures was obtained for each peripheral RNFL, and the results were expressed as an average over 4 quadrants, 12 clock hours, and the mean thickness of the entire circumpapillary scan.

RNFL thickness in superior sector (Sup RNFL), inferior sector (Inf RNFL) and the total average of both sectors (Avg RNFL) are expressed in μm.

3.2. Statistical Analysis

Statistical Package for the Social Sciences windows version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. The association between changes in glucose levels and OCT variation was investigated using univariable and multivariable regression analyses. Student's t-test was used for normally distributed variables. Pearson's correlation analysis was applied to analyze the relationship between variables. The HbA1c values of each group were averaged and expressed as mean ± SD. Significance of the study parameters between three or more groups of data were analyzed by one-way ANOVA. Multivariable logistic regression models were used after controlling for the same sets of confounders. A value of $P < 0.05$ was considered significant.

4. Results

There were 55 participants of male 30 (55 %) and female 25 (45%) enrolled in the study. The mean and standard deviation of diabetic cases was 62.7 ± 7.50 years with sample space of 40 to75 years. The 40 diabetic patients consisted of 20 male (age 56.27 ± 2.01years) and 20 female (age 52.24 ± 3.21 years). The mean age of the 15 healthy control subjects was age 59.3 ± 9.20 years with range of 40 to 75 years. In the group of 15 healthy control 7 were male with age 51.30 ± 4.20 years and 8 females with age 52.41 ± 1.230 years.

Demographic, systemic, and ocular characteristics of the diabetic versus non-diabetic patients revealed that there was non-statistically significant difference as regards age, systolic and diastolic systemic hypertension, BCVA, central corneal thickness (0.062, 0.019, 0.054,0.158, 0.161) between diabetic and non-diabetic patients. There was a statistically significant differences as regard body mass index, smoking states, HDL cholesterol, LDL cholesterol, triglyceride, HBA1c, and intraocular pressure between diabetic and non-diabetic patients (<0.001).

Characteristics	Diabetes[b] (n=80)	Control (n=30)	P-value[a]
Demographic features			
Mean age in years (SD)[c]	62.7 (7.5)	59.3 (9.2)	0.062
Male participants, n (%)	40 (50.0)	15 (50.0)	0.064
Body mass index, kg/m² (SD)	25.4 (3.2)	22.0 (2.8)	<0.001#
Weight, kg (SD)	61.26 (11.8)	55.0 (10.3)	<0.001#
Height, cm (SD)	169.6 (9.3)	158.0 (9.1)	<0.001#
Smoking status, n (%)			<0.001#
Non- smokers	29.7	21.2	
Current smokers	42.0	6.0	
Systemic features			
Hypertension, n (%)	55.2	45.9	0.021
Systolic BL P, mmHg (SD)	131.3 (14.2)	125.1 (15.1)	0.019
Diastolic BL P, mmHg (SD)	72.3 (12.1)	71.4 (12.1)	0.054
HDL cholesterol, mg/dL (SD)	74.1 (11.8)	52.0 (11.5)	<0.001#
LDL cholesterol, mg/dL (SD)	1289.3 (32.2)	114.6 (28.6)	<0.001#
Triglyceride, mg/dL (SD)	118.0 (73.6)	97.0 (68.3)	<0.001#
HbA1c, % (SD)	6.9 (1.4)	5.2 (0.1)	<0.001#
Fasting glucose, mg/dL (SD)	136.2 (32.1)	98.3 (4.2)	<0.001#
Postprandial glucose , mg/dL (SD)	160.4 (42.2)	97.1 (13.3)	<0.001#
Ocular features			
BCVA Log MAR (SD)	0.25 (0.21)	0.19 (0.13)	0.158
CCT, µm (SD)	555.4 (45.1)	552.0 (56.1)	0.161
Intraocular pressure, mmHg (SD)	18.1 (1.6)	15.2 (3.7)	<0.001#7

Table 1: Demographic, Systemic, and Ocular Characteristics of the Participants According to their Diabetic Status

[a]Values are presented as the means (SDs) for continuous variables and percentages for categorical variables.
[b]Diabetes was defined as self-reported anti-diabetic medication use, physician-diagnosed diabetes, or HbA1c≥6.5%.
[c]All values other than age were adjusted for age and sex.
#Statistically significant value at P<0.001.

HbA1c = Glycosylated hemoglobin A1c; HDL= high-density lipoprotein; LDL=, low-density lipoprotein; SD= standard deviation, BCVA = Best corrected visual acuity; BL P= Blood pressure, CCT= Central corneal thickness.

Table 2: revealed the comparison between the RNFLT measurement in both eyes of diabetics cases and healthy control subjects. Peripapillary RNFLT was affected in the superior quadrant of both right and left eyes of diabetic patients as compared to healthy subjects.

Parameters (mean)	Group I, healthy controls (n=30)	Group II, diabetic patients (n=80)	p-value
OD RNFLT			
Average (µm)	123.21±11.22	109.42 ±24.12	0.235
Superior (µm)	135.44±12.72	118.53±12.21	<0.001#
Inferior (µm)	130.39±10.21	124.57±13.42	0.621
Temporal (µm)	73.67±8.54	73.11±14.12	0.765
Nasal (µm)	94.111±13.32	79.61±17.301	0.276
OS RNFLT			
Average (µm)	121.16 ± 17.24	112.23 ± 15.24	0.683
Superior (µm)	124.15±15.36	119.67±10.20	<0.001#

Inferior (µm)	125.91±12.26	126.06±14.31	0.968
Temporal (µm)	74.12±10.36	72.48±10.11	0.593
Nasal (µm)	856.79±14.04	81.04±15.33	0.329
The present data demonstrate significant thinning in retinal nerve fiber layer in patients with HbA1c ,7% (controlled DM). This reduction was increased in patients with HbA1c $7% (uncontrolled DM), in accordance with previous studies (Table 3).18,21			

Table 2: RNFLT in Four Quadrants in Diabetic Patients Compared to Healthy Controls

Table 3: demonstrated significant thinning in retinal nerve fiber layer in patients with HbA1c less than 7% (controlled DM). This reduction was increased in patients with HbA1c equal or more than 7% (uncontrolled DM) in relation to glycemic control.

Parameters	**Control + subgroup 1 (n= 76[30+46]) HbA1c < 7%**	**Subgroup 2 (n=34) HbA1c ≥7 %**	***p*-value**
OD RNFLT			
Average (µm)	123.21 ± 13.42	108.17±12.23	<0.001#
Superior (µm)	129.17±11.51	115.19±11.51	<0.001#
Inferior (µm)	131.66±12.79	123.20±17.67	<0.001#
Temporal (µm)	77.30±11.17	75.69±9.89	0.611
Nasal (µm)	89.74±14.47	84.75±11.29	0.216
OS RNFLT			
Average (µm)	113.21 ±15.12	102.21 ±14.32	<0.001#
Superior (µm)	129.13±13.04	117.13±11.40	<0.001#
Inferior (µm)	129.96±14.10	122.19±17.50	<0.001#
Temporal (µm)	73.83±10.07	69.19±10.39	0.177
Nasal (µm)	85.43±14.94	83.69±16.49	0.697
Notes: Data presented as mean ± standard deviation. #Statistically significant value at <0.001. **Abbreviations:** HbA 1c, glycosylated hemoglobin; OD, right eye; OS, left eye; RNFLT, retinal nerve fiber layer thickness.			

Table 3: Comparison between Peripapillary RNFLT and Glycemic Control in all Four Quadrants

Table 4: revealed that the reduc¬tion in RNFLT was affected in the superior quadrant of both right and left eyes of diabetic patients by the duration of diabetes.

Parameters	**Group II DM <10y (n=45)**	**Group II DM >10 (n=35)**	***p*-value**
OD RNFLT			
Average (µm)	117,26 ±15.41	110.32 ±21,35	0.345
Superior (µm)	126.38±16.65	116.67±14.05	<0.001#
Inferior (µm)	132.13±13.83	121.47±18.78	0.204
Temporal (µm)	77.50±13.87	76.60±10.11	0.839
Nasal (µm)	90.38±10.77	82.93±9.02	85.453
OS RNFLT			
Average (µm)	114.43 ±12.31	108.32 ±15.22	0.213
Superior (µm)	125.75±14.71	115.67±12.32	<0.001#
Inferior (µm)	132.63±13.78	123.20±18.21	0.114
Temporal (µm)	76.19±10.32	70.67±9.48	0.133
Nasal (µm)	83.63±17.61	82.47±15.52	0.848
Notes: Data presented as mean ± standard deviation. #Statistically significant value at P<0.001#. **Abbreviations:** DM, diabetes mellitus; OD, right eye; OS, left eye; RNFLT, retinal nerve fiber layer thickness.			

Table 4: Comparison between Peripapillary RNFLT and Dm Duration (Years)

Table 5: demonstrated that the peripapillary RNFLT was negatively correlated with HbA1c in the supe¬rior, inferior, and nasal quadrants, while it was positively correlated in the temporal quadrant.

Parameters (mean)	*r* (Pearson's correlation)	*p*-value
OD RNFLT		
Average (µm)	-0.242	0.342
Superior (µm)	-0.485	<0.001#
Inferior (µm)	-0.196	0.138
Temporal (µm)	0.084	0.641
Nasal (µm)	-0.214	0.404
OS RNFLT		
Average (µm)	-0.231	0.345
Superior (µm)	-0.392	<0.001#
Inferior (µm)	-0.060	0.640
Temporal (µm)	0.025	0.844
Nasal (µm)	-0.068	0.597
Note: #Statistically significant value at P<0.001. **Abbreviations:** HbA1c, glycosylated hemoglobin; OD, right eye; OS, left eye; RNFLT, retinal nerve fiber layer thickness.		

Table 5: Correlation between Glycemic Control (HbA1c) and Peripapillary RNFLT in Four Quadrants

5. Discussion

Diabetic retinopathy is the most common complication of DM, with significant implication on visual acuity being the leading cause of deterioration of visual loss. However, recent studies have revealed the affection of visual functions, contrast sensitivity, dark adaptation, and decreased amplitudes of VEP, even before the appearance of any impairrment of DR. Thus, early neurodegenerative deterioration had been proven to occur before the onset of DR and subsequently play an effective role in visual deterioration in patients with type 2 diabetes mellitus without DR [20-26].

The hallmark of retinal neurodegeneration is apoptosis of retinal ganglion cells with axonal degeneration and reactive gliosis of astrocytes, such changes lead to thinning of retinal inner layers [27,28]. RNFL thinning in diabetics patients was first demonstrated by Chihara et al. Skarf B. then identified RNFL thinning as an early marker of diabetic rertinopapthy [29,30].

The mechanisms of retinal neuro-degeneration in diabetic patients are complex, hyperglycemia promotes optic nerve hypoperfusion through multiple factors such as advanced glycation end products, increased oxidative stress and angiogenic factors, resulting in alteration of the retinal microenvironment and a cascade of events ending with ganglion cell apoptosis, hence fluctuation of blood glucose is more likely to cause structural nerve damage even before causing significant vision changes in early stages of DM [31].

Neurodegenerative changes may also be caused by ischemia since inner retinal layers are more liable to hypoxia and ischemia in comparison to outer retinal layers supplied directly from the choroid. Ocular ischemia followed by reperfusion and increased oxidative stress can induce ganglion cell apoptosis in diabetics [32].

In the current study, average RNFL thickness as well as superior and inferior RNFL thickness were significantly lower in the uncontrolled DM group, this is consistent with findings in prior studies using different SD-OCT devices such as Spectralis Domain OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany), Stratus OCT (Carl Ziess Meditech, Dublin, CA, USA), Cirrus SD-OCT (Carl Zeiss Meditech, Dublin, CA, USA) [33-35]. An another study showed that only superior quadrant peripapillary RNFL thickness was slightly less in diabetic patients than normal subjects [36].

In a meta-analysis by Chen X et al., peripapillary RNFL thickness was significantly reduced in diabetic patients without DR in comparison to age matched healthy controls [37]. In contrast, Srinivasan et al., in two different studies found no significant difference between healthy individuals and diabetics with or without DR in any quadrant [38,39].

The present study revealed that peripapillary RNFLT was affected in the superior quadrant of diabetic patients in relation to glycemic control as compared to healthy subjects. This is consistent with the outcome of previ¬ous studies, which demonstrated that RNFLT was decreased in patients with preclinical DR in all four quadrants, but the difference was significant only at the superior quadrant [40,41].

RNFLT reduced more in oral hypoglycemic users, which is consistent with previous studies [41,42]. Hammes et al., described that diabetes can induce apoptosis in retinal ganglion cells and Müller cells in an experimental diabetes model, and this supports

the present findings of that RNFLT was decreased prior to the development of DR [41].

Also, the present study data demonstrate significant thinning in retinal nerve fiber layer in patients with HbA1c < 7% (controlled DM). This reduction was increased in patients with HbA1c >7% (uncontrolled DM) in relation to glycemic control, in accordance with previous studies [41,42].

The present study revealed that peripapillary RNFLT was negatively correlated with HbA1c in the average, supe¬rior, inferior, and nasal RNFLT quadrants, while it was positively correlated in the temporal quadrant. This correlation was significant in the superior quadrant only, which is consistent with the findings by Srivastav et al. [43].

The present study provided evidence that the positive relationships between hyper-glycaemic status and RNFL thickness were significant, even after controlling for CCT. Increases in CCT may lead to overestimated values, and diabetic patients have relatively greater CCTs due to the osmotic gradients induced by accumulated sorbitol in the cornea [43].

Worse glycemic control contributed to reduced retinal neurovascular coupling in patients with clinical signs of DR. Progression of neurovascular dysfunction in DR might be related to structural degeneration of the neurovascular complex in the inner retina [44].

6. Conclusion

Impairment of glycemic control affects the peripapillary RNFLT mainly in the superior quadrant in diabetic type 2 patients. This thickness also tends to be decrease with long-standing DM, and development of DR. Peripapillary RNFLT may be used as a predictive marker of retinopathy devel¬opment, which might help to avoid future complications.

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