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Effect of Glycated Hemoglobin Levels on Intraocular Pressure in Patients with Diabetes Mellitus in Saudi Population

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ABSTRACT

Aim of the study was to investigate the effect of chronic hyperglycemia as determined by high glycated hemoglobin (HbA1c) on intraocular pressure (IOP) in patients with diabetes and to recognize the diabetic patients at high risk of developing glaucoma in a tertiary care hospital in western region of Saudi Arabia.This was a retrospective chart review performed at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Hospital records of diabetic patients in the department of ophthalmology from August 2015 to June 2020 were collected. Patients diagnosed with glaucoma, using intraocular pressure-lowering medications, or using topical or oral steroids were excluded from the study.Overall, 159 participants were enrolled in the study. A significant association between high HbA1c levels and IOP values was observed. Individuals with HbA1c below 6.5, between 9.6 to 10.5, and over 12.6 had a mean IOP of 15.2 ± 2.87, 16.6 ± 5.12, and 19.5 ± 1.88, respectively (p= 0.031). Longer diabetes duration was associated with a higher IOP (p=0.028). Another finding illustrated that female participants had significantly higher IOP compared to males (16.94 ± 3.25 mm Hg, 15.15 ± 3.31 mm Hg, p=0.001, respectively). A significant positive association between high HbA1c levels and IOP values was found, which indicates that diabetes and elevated HbA1c are significant contributing factors for elevated IOP. There was a statistically significant higher IOP in females in which further research is needed with prospective and extensive data collection. Accordingly, a regular diabetic eye examination to monitor intraocular pressure is recommended specially to those with uncontrolled diabetes and high HgA1c to reduce ocular morbidity due to glaucoma.

KEY WORDS: DIABETES; INTRAOCULAR PRESSURE; GLAUCOMA, GLYCATED HEMOGLOBIN.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease associated with chronic hyperglycemia (Mayer-Davis et al .2018). It is a distressing epidemic and is considered one of the leading causes of death worldwide (Glovaci et al. 2019). Globally, the prevalence of DM is estimated to be 9.3% (463 million people) in 2019, increasing to 10.2% (578 million)and 10.9% (700 million) by 2030 and 2045, respectively, with more than 29% incidence in Saudi Arabia alone from 1990 -2015 (Saeedi et al. 2019) (Alotaibi et al. 2017). DM is diagnosed according to plasma glucose criteria in the form of fasting plasma glucose (FPG) levels, 2-h plasma postprandial glucose (2-h PPG) levels, or the glycosylated hemoglobin (HbA1c) criteria reflecting the average plasma glucose concentration over the previous 8–12 weeks (Care 2019) (Nguyen et al.2019). The International Expert Committee recommends HbA1c as a reliable tool for diagnosing type 1 and type 2 DM with a cutoff point of ≥6.5% (Nathan et al. 2009). Al Salamah et al.(2020) have reported that 35% of Saudis aged 55 or more had type 2 diabetes.

HbA1c testing has multiple advantages over plasma glucose measurement, such as pre-analytical stability and less day-to-day variation due to stress or illness (Nathan et al.2009). Therefore, HbA1c is the gold standard for diabetes control. Besides reflecting the glycemic adjustment, Hba1c is used as a predictor 1to assess secondary microvascular complications, including retinopathy, neuropathy, and nephropathy in cases of insufficient glycemic control (Hasselacher et al. 2014). Diabetes contributes to the risk of developing several types of glaucoma, most commonly, primary open-angle glaucoma (POAG) and neovascular glaucoma (NVG) (Resnikoff et al.2004 Barac et al. 2015, Bahera et al .2020).

POAG is a multifactorial disease that is caused by retinal ischemia, remodeling of the optic nerve head, and altered trabecular meshwork function(Feki et al. 2019) (Faralli et al. 2019) . Diabetic patients are susceptible to retinal ischemia, which is believed to be the main cause of neovascular glaucoma by stimulating the release of vascular endothelial growth factor-A (VEGF-A), leading to vasodilatation and increasing blood flow, which initiates new blood vessel formation leading to NVG (Hayreh 2007, Yang et al .2018). Glaucoma is defined as a group of ocular disorders that are characterized by progressive optic neuropathy and associated visual field loss (Bertaud et al. 2019). Although treatable, it is the most common irreversible blinding disease worldwide (Quigley et al. 2006). Therefore, early detection is required for a good prognosis. Normal intraocular pressure (IOP) is 10-21 mm Hg, which is preserved by a balance between the aqueous humor production and drainage. Any imbalance leads to elevated IOP (Khaw and Elkington 2004), causing both vascular and mechanical stresses (Song et al. 2016) .Therefore, it is an important risk factor for glaucoma deterioration and progression, and currently, is the only modifiable factor (Asal et al. 2020).

A recent meta-analysis evaluated 47 studies from 16 different countries and found that patients with diabetes had been associated with an average of 0.18 mmHg increase in the IOP (Zhao et al. 2014) Furthermore, other studies found that patients with increased levels of HbA1c had substantially higher IOP levels compared to the patients with lower levels of HbA1c (Hymowitz et al. 2016, Perez-Rico et al. 2015, Takahashi et al. 2020).

A study conducted in Riyadh, Saudi Arabia, found that diabetic patients had higher IOP compared to non-diabetic subjects. HbA1c was used as a criterion for diagnosing diabetes; however, the relationship between HbA1c value and IOP has not been studied (Briggs et al. 2016). To the best of our knowledge, there have been no reports evaluating the relationship between HbA1C and IOP among the Saudi population. Therefore, we aimed to investigate the effect of chronic hyperglycemia as determined by HbA1c on IOP in patients with diabetes and identify diabetic patients at risk of developing glaucoma in Saudi Arabia from 2015 to 2020.

MATERIAL AND METHODS

Study design and setting: This retrospective chart review study was conducted at King Abdul-Aziz University Hospital (KAUH), a tertiary center in Jeddah, Saudi Arabia. Medical records from glaucoma and retina clinics in the Department of Ophthalmology between August 2015 and June 2020 were collected.

Sample criteria and diagnostic instrument: Patients aged 15-90 years diagnosed with type 1 or type 2 DM were included Patients diagnosed with glaucoma, using IOP-lowering medications, or using topical or oral steroids were excluded from the study. Of the 383 diabetic patients treated at the department of ophthalmology between 2015 to 2020, 224 subjects were excluded: 73 diagnosed with glaucoma, 138 with previous history of laser or intraocular surgery, and 13 on IOP-lowering medications or topical steroids. Thus, 159 subjects met the inclusion criteria and were enrolled in the study.Data obtained from medical records included demographic data such as age, sex, and nationality. Additionally, type and duration of diabetes, HbA1c levels, IOP in the right and left eye (IOP-OD, IOP-OS, respectively), and body mass index (BMI), which was calculated as weight in kilograms divided by height in meters squared were also collected.

The patient's IOP was measured using a Goldmann applanation tonometer. The mean IOP was calculated for each patient as the sum of the pressure of both eyes divided by two, using an excel equation. Glycemic control measurement (HgA1c), was obtained within one year before or after IOP measurement. Patients were categorized according to their glycemic control in three categories: good glycemic control (HbA1c <7%), moderate glycemic control (HbA1c 7-9%), and poor glycemic control (HbA1c >9%) (23). Diabetes duration was defined as the period from the first diagnosis to the day of IOP measurement.

Analysis:Data were registered using an online Google form, and was then imported to Microsoft Excel 2020 for data entry. Statistical analysis was performed using the Statistical Package for the Social Sciences IBM© SPSS© version 21 (IBM© Corp., Armonk, NY, USA). Descriptive statistics (mean and standard deviation) were calculated for normally distributed variables including IOP, HbA1c, BMI, age, and diabetes duration. Frequencies and percentages were calculated for sex, nationality, diabetes type, and population categories. We used the Shapiro-Wilk test to check for normality. An independent-samples t-test was used to compare the IOP in both sexes and both types of diabetes. For multiple comparisons with the IOP, one-way analysis of variance (ANOVA) was performed. All P-value < 0.05 were considered to be statistically significant. Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Research ethics: This research was approved by the Biomedical Ethical Committee at KAUH (ref: 653-19).

RESULTS AND DISCUSSION

There were 73 (45.9%) men and 86 (54.1%) women. The mean age was 58 ± 16 years, with the majority of patients being 50 to 69 years old (49.1%). The majority of patients, 82 (51.6%), were type 2 diabetic patients. The characteristics of the study population are shown in Table 1.

Table 1. mean and standard deviation of the study population characteristics

Characteristics	N(%)	Mean ± SD	IOP (mm hg)	
			Mean ± SD	p-value
Gender				
Male	73 (45.9%)		15.15 ± 3.31	0.001
Female	86 (54.1%)		16.94 ± 3.25	
Diabetes type				
Type 1	77 (48.4%)		16.38 ± 3.14	0.347
Type 2	82 (51.6%)		15.87 ± 3.60	
BMI classifications	4 (2.5%)	17.53 ± 0.64		0.77
Underweight	34 (21.7%)	22.49 ± 1.57		
Normal weight	38 (24.2%)	27.51 ± 1.43		
Pre-obesity	81 (51.6%)	35.55 ± 4.76		
Obesity				
Age classifications				
<29 y	15 (9.4%)	23.47 ± 3.96		0.42
30 – 49 y	23 (14.5%)	42.04 ± 5.42		
50 – 69 y	78 (49.1%)	60.90 ± 5.08		
70 – 84 y	43 (27.0%)	75.91 ± 4.84		

Female participants had statistically higher IOP compared to the male participants (16.94 ± 3.25 mm Hg, 15.15 ± 3.31 mm Hg, respectively, p=0.001). We observed no significant difference between Type 1 as well as Type 2 DM and IOP (16.38 ± 3.14, 15.87 ± 3.60, respectively), p=0.347. When we classified diabetic patients according to their glycemic control, 72 participants (46.5%), almost half of the sample, had moderate glycemic control. The mean HbA1c for good, moderate, and poor controls was 6. ± 1.01, 8.05 ± 0.58, and 10.80 ± 1.40. respectively. The mean IOP was elevated in the poor glycemic control patients (16.78 ± 3.65 mmHg) compared to those with good glycemic control (15.65 ± 3.08 mm Hg). The difference was not statistically significant (p=0.263). Table 2 shows a comparison between the three groups.

There was a statistically significant difference between the HbA1c range groups and IOP, as determined by one-way ANOVA (F [7,149] = 2.276, p = 0.031). Subjects with HbA1c above 12.6 displayed higher IOPs (19.58 ± 1.88 mm Hg), compared to the subjects with HbA1c between 6.5 to 7.5 (15.52 ± 3.89 mm Hg), and between 7.6 to 8.5 (16.029 ± 2.81 mm Hg), with a mean difference of (4.05 mm Hg), (p=0.006) and (3.55 mm Hg), (p=0.017), respectively (Figure 1). One-way ANOVA revealed that with longer duration of diabetes, the IOP significantly increased as well (F (3,143) = 3.117, p = 0.028). Thus, participants with a diabetes duration of less than five years had a mean IOP of 14.75 ± 2.99 mm Hg, while participants with a diabetes duration ranging from 11 to 20 years had a mean IOP of 16.93 ± 3.79 mm Hg, with a mean difference of (2.21 mm Hg), (p=0.006). Table 3 presents the mean IOP values according to the duration of DM.

In this study, we found that individuals with higher levels of HbA1c exhibited significantly higher IOP levels compared to individuals with lower HbA1c levels. This

result is consistent with those of previously published studies, (Kang et al. 2019,Takahashi et al. 2020). Hymowitz et al.2016 found an association between poor glycemic control, as evidenced by higher HbA1c and elevated IOP. Baisakhiya et al. 2017 observed an association between higher HbA1c and raised IOP, reporting that poor glycemic control is a risk factor for glaucoma in diabetic patients.

The underlying pathogenesis that explains how DM promotes increased IOP remains unclear. Diabetes is a known cause of microvascular damage and can disturb blood flow at the level of the optic nerve head and retina, which stimulates the invasion of the iris surface and iridocorneal angle of the anterior chamber by a fibrovascular membrane. This fibrovascular membrane initially resists the aqueous outflow, resulting in open-angle glaucoma, and later obstructs the angle and produces secondary angle-closure glaucoma, (Hayreh 2007,Salzy et al.2009, Grzybowski et al. 2020). In addition, higher glucose levels in the aqueous humor of diabetic patients have been observed to upregulate and promote the accumulation of extracellular matrix proteins, particularly fibronectin, thereby blocking aqueous drainage, leading to an increase in IOP. Chronically raised IOP levels sequentially lead to optic nerve head damage, stemming from progressive mechanical compression (Faralli et al .2019).

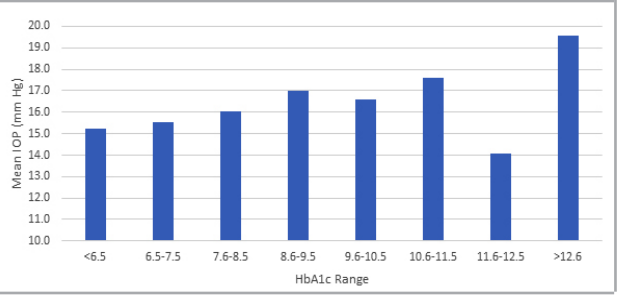
Table 2. mean and standard deviation of HgA1c and IOP in glycemic control groups

	good glycemic control: N (%)38 (24.5%) Mean ± SD	moderate glycemic control: N (%)72 (46.5%) Mean ± SD	poor glycemic control: N (%) 45 (29%) Mean ± SD	p-value
HbA1c	6.006 ± 1.014	8.052 ± 0.581	10.809 ± 1.405	0.001
IOP	15.65 ± 3.08	15.91 ± 3.39	16.78 ± 3.65	0.263

Table 3. Mean and standard deviation of IOP according to duration of DM

Diabetes duration	N(%)	Mean ±SD	Mean IOP (mmHg) ±SD	P value
<5 y	26 (17.7%)	2.04 ± 1.34	14.75 ± 2.99	0.028
5 – 10 y	33 (22.4%)	8.91 ± 1.73	15.74 ± 2.45	
11 - 20 y	57 (38.8%)	16.25 ± 2.708	16.93 ± 3.79	
21 – 33 y	31 (21.1%)	24.58 ± 3.09	16.82 ± 3.46	

Figure 1: Comparison between HgA1c range and IOP



Oshitari et al. (2007) found a significant association between IOP and glycemic control categories, which is inconsistent with our result, as we could not find an association between glycemic control categories and IOP levels. This is probably due to the use of different HbA1c classifications. Moreover, some researchers have found an alteration in the IOP values following transient blood glucose fluctuations in cases of hypoglycemia or postprandial hyperglycemia that cannot be measured by HbA1c (Rihan et al.2020). Additionally, comorbidities that falsely lower HbA1c levels on test results by shortening the erythrocyte survival rate could potentially affect the outcome of the study (Report 2011, Ang et al. 2014).

Our study showed that people with a longer duration of diabetes had higher IOP values compared to patients with a shorter duration. In contrast, a previous study conducted in Riyadh, Saudi Arabia, stated that the duration of diabetes did not vary significantly with IOP levels (Briggs et al. 2016). Recall bias of diabetes duration plays a major role in the inconsistency between the two results. Further, a meta-analysis study reported that each year since diabetes diagnosis increases the risk of glaucoma by 5% (95% CI, 1%–9%), which may be due to the cumulative neuronal damage that progresses with time, (Zhao et al. 2015, Grzybowski et al .2020).

Moreover, we found that female participants had a higher IOP than males, a difference which was statistically significantly. Moreover, Kang et al.2019 reported a significant relationship between IOP and HgA1c in female without diabetes. In contrast, Hymowitz et al.2016 reported no significant difference between two sexes regarding IOP levels. However, variability in the results

could stem from differences in the male-to-female ratio between the two sample populations. The sex-related differences in IOP measurement remain incompletely understood. Previous studies reported that anatomical and structural eye differences between the two sexes made the comparison inaccurate, which explains part of this discrepancy (Patel 2018, Chua et al. 2019).

Limitations: This retrospective record review study encountered a few inherent limitations. First, it was not possible to provide precise HbA1C levels and random blood glucose at the exact time point during which the IOP was measured. In addition, open-angle glaucoma has no symptoms initially prior to peripheral vision loss; therefore, many diabetic patients had already presented with glaucoma due to delayed periodic eye screening.

Recommendation Planning an educational campaign empowering diabetic people to perform periodic eye screening for monitoring IOP to ensure that glaucoma can be diagnosed in the early stage and effectively treated. Further, future studies to assess the confounding factors that may influence the association between HbA1C and IOP, such as central corneal thickness and lens status are warranted.

CONCLUSION

The current study found a significant association between high HbA1c levels and IOP values, which indicates that diabetes and elevated HbA1c are significant contributing factors for elevated IOP. Therefore, a well-established diabetic screening program includes IOP measurement should be applied routinely. Accordingly, diabetics with uncontrolled blood sugar and high HgA1c are recommended to undergo more frequent eye examination to monitor IOP to reduce ocular morbidity due to glaucoma.

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