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The Correlation Between Intraocular Pressure and Glycated Haemoglobin A1c Test Results in Diabetic and Nondiabetic Subjects

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Abstract

Introduction. Diabetes mellitus is a worldwide disease of high incidence and prevalence, in addition, it is associated with a number of ocular complications, which threatens vision if not identified and treated properly like retinopathy, neovascular glaucoma, vitreous hemorrhage, and it is a suggested risk factor for other conditions like primary open angle glaucoma.
Purpose. To study the correlation of intraocular pressure with HbA1c test results in a sample of diabetic and non-diabetic patients.
Materials and methods. Case control study conducted on a total of 240 subjects, 120 type 2 diabetic patients and 120 non diabetic healthy subjects, the sample collected from 1/5/2017 to 1/7/2018, permission obtained from each patient to participate in the study, and complete ophthalmological examination, intraocular pressure measurement, blood test for HbA1c was done, both eyes of each patient were included in the study, equal numbers of males and females were included to avoid gender bias, the sample was rearranged according to HbA1c levels into four groups which are: non diabetic group, pre diabetic group, diabetic well control and poor control groups, their numbers respectively were 102, 18, 40, 80.
Results. By comparing the mean age value between diabetic and control groups no major difference was found, there was statistically significant difference in mean intraocular pressure, HbA1c between diabetic and control groups. Pearson correlation showed positive linear relationship between intraocular pressure and HbA1c in diabetic group, $r=0.60$, $P<0.05$, while in control group there was no relationship between the variables, $r=0.06$, age again was not significant among the four groups, while intraocular pressure means was significantly different when we used analysis of variance, $P<0.001$, scatter plots showed some linear scatter and uphill distribution only in group 2 (poor control diabetic patients).
Conclusion. Diabetic patients showed high mean intraocular pressure compared to non-Diabetic patients, with positive correlation between intraocular pressure and the level of HbA1c exist in the Diabetic group and the strongest correlation was found among the poor control diabetic group.
Keywords: intraocular pressure, Glycated haemoglobin A1c, DM, non-diabetic subjects, primary open angle glaucoma, vitreous hemorrhage

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Корреляция между внутриглазным давлением и результатами теста на гликированный гемоглобин A1c у пациентов с и без диабета

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Резюме

Введение. Сахарный диабет является всемирно распространенным заболеванием с высокой степенью заболеваемости и частотой встречаемости. Кроме того, он связан с рядом осложнений, которые представляют опасность для зрения, если их не выявить и не лечить должным образом, например, ретинопатией, неоваскулярной глаукомой, кровоизлиянием в стекловидное тело. Это также предполагаемый фактор риска других состояний, таких как первичная открытоугольная глаукома.
Цель. Изучить корреляцию внутриглазного давления с результатами теста на HbA1c у пациентов с и без диабета.
Материалы и методы. Исследование «случай – контроль» проводилось в общей сложности 240 пациентам, из них 120 – с диабетом 2-го типа и 120 – без диабета, выборка была собрана с 01.05.2017 по 01.07.2018, от каждого пациента было получено разрешение на участие в исследовании, проведен полный офтальмологический осмотр (измерение внутриглазного давления, анализ крови на HbA1c, в исследование были включены оба глаза каждого пациента). Мужчин и женщин было равное количество, это необходимо было, чтобы избежать гендерной предвзятости. Выборка была перераспределена в соответствии с уровнем HbA1c в четыре группы: 1) группа без диабета, 2) группа преддиабета, 3) диабетическая группа «хорошего» контроля и 4) диабетическая группа «плохого» контроля. Количество пациентов соответственно составило 102, 18, 40 и 80.
Результаты. Между диабетической и контрольной группами при сравнении среднего значения возраста не было обнаружено значительной разницы, но была статистически значимая разница в среднем внутриглазном давлении и HbA1c. Корреляция Пирсона показала положительную линейную связь между внутриглазным давлением и уровнем HbA1c в группе диабетиков ($r=0,60$, $P<0,05$), в то время как в контрольной группе не было никакой связи между переменными ($r=0,06$). Возраст снова не был значимым среди четырех групп, в то время как средние значения внутриглазного давления значительно различались при использовании дисперсионного анализа ($P<0,001$).
Заключение. У пациентов с диабетом отмечено высокое среднее внутриглазное давление по сравнению с пациентами без диабета, при этом положительная корреляция между внутриглазным давлением и уровнем HbA1c существует в группе диабетиков, а самая сильная корреляция обнаружена среди пациентов с диабетом из группы «плохого» контроля.

Ключевые слова: внутриглазное давление, гликированный гемоглобин A1c, сахарный диабет, пациенты без диабета, первичная открытоугольная глаукома, кровоизлияние в стекловидное тело

■ INTRODUCTION

Diabetes Mellitus is a common chronic disease with reported increase in incidence in recent years, the prevalence of this chronic disease estimated to be 2.8% in 2000, and expected to be 4.4% in 2030 [1]. The highest rates of diabetes are currently in the Eastern Mediterranean and Middle East with North and South America close behind, and the most affected age group is currently in the 40–59 year, tissue complications of diabetes can be specific, microvascular damage to the eye, kidney or peripheral nerve, or non-specific macro-vascular accelerated atherosclerosis, conclusive evidence now links the level of hyperglycaemia to development of microvascular complications, by several potential mechanisms Each of these processes results in the generation of reactive oxygen species, so oxidative stress may represent the final common path towards complications [2].

Several studies demonstrated also an association between diabetes and high intraocular pressure levels and thus high risk for glaucoma as compared to non-diabetic controls [3–5].

Glaucoma is a progressive optic neuropathy associated with typical optic disc changes and visual field defects, elevated intraocular pressure is the major risk factor for glaucoma even though large proportion of glaucoma patients associated with normal intraocular pressure, still controlling intraocular pressure is the treatment target in glaucoma, many risk factors has been described in association with primary open angle glaucoma including, old age, myopia, family history, worldwide, the incidence of glaucoma is around 2.5 million per year and the prevalence of blindness due to primary open angle glaucoma is around 3 million [6].

One of the underlying mechanisms explained by in vitro study showed an association between high glucose concentration in aqueous humor and excess extracellular matrix synthesis of fibronectin in trabecular meshwork-characteristic feature of the outflow system in POAG [7].

In addition to that, cultured HTMC when exposed to high glucose concentration environment it was found that Nitric oxide production decreased accompanied with increased superoxide production. Thus hyperglycemia induces oxidative stress in HTMC and may cause cellular dysfunction and damage of the trabecular meshwork [8].

Abnormalities of retinal vascular and retrobulbar circulation has been identified in both diabetes and glaucoma, this may help understand the relationship between the two diseases, microvascular damage in diabetes with associated early increase in retinal capillary blood flow (due to loss of autoregulation) this will creates mechanical stress that leads to endothelial separation and more pericyte loss and will affect the blood supply to anterior optic nerve and retina [12]. Disturbances in auto-regulation of posterior ciliary circulation (mainly increase central retinal vein flow) has been found in diabetes [9].

For glaucoma, a study showed that retrobulbar blood flow velocities were lower and resistivity indices were higher in all retrobulbar vessels in ocular hypertensive patients than in normal subjects and in glaucoma patients than in normal subjects, Glaucoma

patients had lower end-diastolic velocities and higher resistivity indices than did normal subjects in the ophthalmic and posterior ciliary and central retinal arteries [10].

On another study, glaucoma subjects had a significantly lower retinal blood volume, flow, and velocity than the control subjects at the two superior and inferior retinal locations [11], so this compensatory vascular response found in early glaucoma contributes to optic nerve damage through vasoconstriction.

One of the theories explaining the underlying mechanism of vascular dysregulation in both diseases is based on nitric oxide and endothelin-1 role, NO produced by endothelial cells nitric oxide synthase, because nitric oxide synthase activation is under insulin control and is important vascular regulator, reduced sensitivity of endothelial cells in addition to reduced synthesis of nitric oxide the important vascular dilator is found in type 2 diabetes and vasoconstriction of retinal vasculature is the result of this, contributing to ischemic changes in diabetes as the disease progress [12].

Many studies compared the levels of NO in aqueous humor of patients with and without glaucoma and found levels to be significantly lower for glaucoma patients [17], the association of endothelial nitric oxide synthase gene polymorphism with the glaucoma disease pathogenesis also studied, this supports the theory of altered NO signaling system in glaucoma and its importance as risk factor for POAG [13].

The effect of NO on Schlemm canal cells, trabecular meshwork cells explained in many studies, one study showed that Inhibition of endogenous NO synthase resulted in a 7% increase in Schlemm Canal cell volume and thus reduction in outflow facility [14]. NO could increase trabecular outflow by increasing the permeability of trabecular cell layer in addition to trabecular meshwork relaxation this was concluded by another study [15].

According to the vascular concept of glaucoma, glaucomatous ganglion cell damage is at least in part caused by chronic impairment of blood supply to the optic nerve head by dysregulation, and it related to an altered endothelial function in the supplying vessels where the constant formation of NO provides the maintenance of a basal vasodilator tone in the optic nerve head, in glaucoma Changes in NO synthesis might therefore shift the delicate balance between vasoconstrictor and vasodilator endothelial agents resulting in altered blood supply [16].

Aqueous ET-1 levels in patients with type 2 diabetes compared with controls was elevated, additionally endothelial dysfunction with alteration in synthesis of these regulatory substances may be responsible for the pathophysiology of diabetic complication [17].

ET-1 is also associated with neuronal apoptosis in central nervous system, in a study it was found that exposing cultured retinal ganglion cells to ET-1 resulted with apoptotic cell death [18]. It was found that Increased ET-1 concentration in the aqueous humor of POAG patients [19]. And their effect on HTMC contractility by a study conducted on glaucoma patients: contraction and relaxation of these cells may influence intra-ocular pressure in the sense that their relaxation makes a trabecular space enlargement and facilitates outflow, while contraction produces the opposite effect [20]. This may provide common mechanism for both diseases but still the full molecular pathology not well established.

Hemoglobin is the oxygen carrying pigment in blood, most hemoglobin is type A, and this type A hemoglobin composed in part of many minor components HbA1a1, HbA1a2, HbA1b, HbA1c,HbA1cis the glucose binding hemoglobin and called glycated or glycosylated hemoglobin, glucose bind to N-terminal amino acid of β-chain of hemoglobin molecule

and forms a Schiff base, this binding is non-enzymatic and continue through the life cycle of Red blood cells, thus testing HbA1c reflects mean glucose concentration over period of 8–12 weeks, so it provides good measure of chronic glycemia and correlate well with long term complications of diabetes than other blood and urinary glucose testing [21, 22].

The ADA recommended by 2010, HbA1c test to diagnose diabetes with cut-point of 6.5%, this cut-point based on analysis of data collected from several studies, levels above 8 % considered unfavorable, with risk of microvascular complications [23].

Advantages of using HbA1c test for diagnosing diabetes include:

- assessment of chronic hyperglycemia over 2–3 months period;
- no fasting is needed;
- individual variability is very low [24].

HbA1c test levels are expressed either as percentage % according to DCCT units [25]. Or it is expressed as millimoles per mole, according to the IFCC units [26], all of these units can be easily converted using one of the online calculators.

HbA1c Range presented as percentage:

- non-diabetes expected range between 4.0–5.6%;
- pre-diabetes range 5.7–6.4%;
- while those with 6.5% or higher HbA1c levels have diabetes [27].

The aim is to study the correlation between intraocular pressure and HbA1c test results in a sample of non-insulin dependent diabetic patients and a sample of non-diabetic patients who visited Ibn Al-Haitham teaching eye hospital which is tertiary centre.

■ MATERIALS AND METHODS

A cross sectional study conducted on a total of 240 subjects (480 eyes in total), 120 (240 eyes) was type 2 diabetic patients 60 females and 60 males and 120 (240 eyes) was non diabetic healthy subjects of 60 females and 60 males, the age group for the collected sample was between 45 years – 70 years.

All visited consultation clinics in Ibn Al Haitham teaching eye hospital which is tertiary centre, for various complaints including ocular discomfort, blurring of vision, red eye complain, during this time no differences in the numbers of examined males and females among diabetic population was noted, these patients were consented and permission obtained for complete ophthalmological examination, intraocular pressure measurement, blood test for HbA1c.

Full examination of anterior segment, posterior segment fundus examination was done, diabetic maculopathy, non-proliferative diabetic retinopathy was included in the study, while proliferative diabetic retinopathy was excluded, other exclusion criteria include history of glaucoma, ocular trauma (penetrating and blunt), pseudoexfoliation syndrome in either eye, mature, intumescent cataract, cataract surgery, intravitreal therapy for diabetic retinopathy and laser retinal photocoagulation.

Intraocular pressure was measured with Goldmann applanation tonometry for all subjects right and left eyes at time of visit. In hospital laboratory unit venous blood obtained from each subject, glycosylated hemoglobin A1c was measured with compact glycohemoglobin analyzer POCKETCHEM A1C machine and the result presented in percentage. According to HbA1c levels we rearranged the sample into four groups which are: non diabetic group, pre diabetic group, diabetic well control and poor control groups, their numbers respectively were 102, 18, 40, 80.

Statistical Analysis

The sample was arranged into diabetic and non-diabetic/control groups. Statistics was done using student T test to compare the means among many variables where P value <0.001 significant, and Pearson correlation coefficient used to find the linear correlation between IOP and HbA1c, where value of r represent the strength of correlation as below: 1.0–0.5 strong positive correlation; 0.5–0.3 moderate positive correlation; 0.3–0.1 weak positive correlation; 0 no correlation

Same goes for negative values and the correlation would be negative correlation.

P value was calculated representing the significance level of Pearson correlation r, and values <0.05 considered significant. Then we rearranged the sample into four groups based on values of HbA1C, and used Analysis of Variance to compare the four group means for statistical significance, then Least Significant Difference was calculated. Scatter plots was created for each of the four groups, in order to do that we needed the values of r square, p value, r square values explain how much variation within the data is explained by the created model and the higher the better, p value represented the significance.

■ RESULTS

The sample was arranged into a group of diabetic patients (Table 1) and a group of non-diabetic (control) (Table 2) subjects. The difference was found to be highly significant (P<0.001) regarding IOP, HbA1c mean values between the two groups, on the other hand age was non-significant.

P value result was <0.00001 and indicate strong significance and r value means strong positive correlation. P value show no significant association, r value of 0.063 mean no correlation in control group was found (Table 3).

We divided the sample into four groups (based on HbA1c value) of non-diabetic, pre diabetic, diabetic (well control and poorly control) (Table 4). Descriptive data and means

Table 1
Descriptive data and means in DM group

DM	Minimum	Maximum	Mean	SE	SD	P-value
Age	45.00	70.00	57.30	0.59	6.55	0.805
IOP	12.50	24.50	17.02	0.26	2.92	0.668
HbAlc	6.5	12.90	8.89	0.16	1.77	0.794

Table 2
Descriptive data and means in control group

Non-DM	Minimum	Maximum	Mean	SE	SD	P-value
Age	45.00	70.00	56.33	0.69	7.65	0.242
IOP	9.00	20.50	13.72	0.16	1.83	0.0001
HbAlc	4.30	6.30	4.95	0.04	0.46	0.0001

Table 3
Show the correlation between IOP, HbA1c in DM and control groups

IOP HbA1c	DM	Control
Pearson Correlation (r)	0.60	0.063
P-value	0.0001	0.980

Table 4
Shows the four groups according to HbA1c level

	HbA1c % range	Note
Group 1	6.5–8.0	Well control DM
Group 2	>8.0	Poor control DM
Group 3	5.7–6.4	Pre-DM
Group 4	≤5.6	No-DM

Table 5
Descriptive data and means of the four groups according to sex

	No.	Male	Female	Mean age	Mean IOP mmHg	Mean HbA1c %
Group 1	40	17	23	56.35	14.55	7.38
Group 2	80	43	37	57.65	18.28	9.80
Group 3	18	9	9	58.50	16.94	5.78
Group 4	102	51	51	55.95	13,16	4.81

of the four groups according to sex (Table 5). The age and sex factor were non-significant among the four groups.

P value indicate high significance, that means at least one of the four groups tested differs from the others significantly, to find that in detail, we applied the LSD test. According to the LSD tests, mean IOP showed highly significant difference among all groups (Table 6, 7).

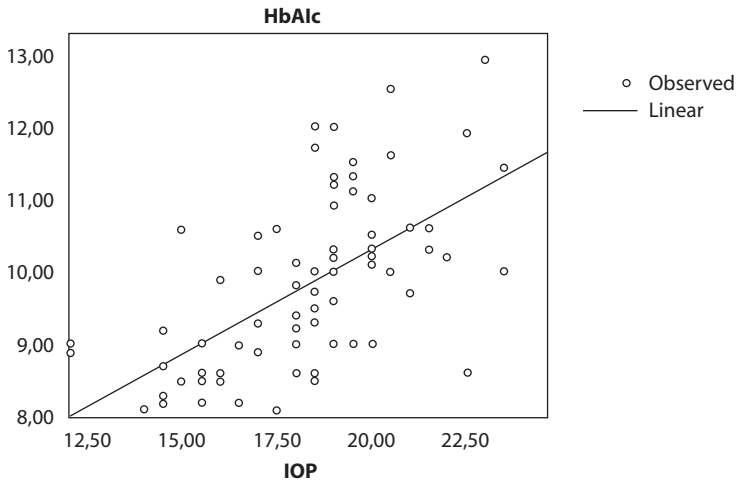
The correlation between IOP and HbA1c is highest in group 2 poor control DM r=0.610, P=0.000 and represented below in scatter plot (Figure).

Table 6
LSD to test the difference/significance in mean IOP of the four groups

Groups 1, 2, 3, 4		Mean Difference	SE	P-value	Sig
1	2	-3.73750-*	.36334	.000	HS
	3	-2.39444-*	.53253	.000	HS
	4	1.38824*	.35003	.000	HS
2	3	1.34306*	.48947	0.007	S
	4	5.12574*	.28021	.000	HS
3	4	3.78268*	.47968	.000	HS

Table 7
Contains the values needed to create scatter plot between IOP and HbA1c for each group

	r/correlation	R square	P value	Significance p<0.05
Group 1	0.014	0.000	0.931	NS
Group 2	0.610	0.372	0.000	HS
Group 3	0.090-	0.008	0.360	NS
Group 4	0.282	0.079	0.004	S



Scatter plot of group 2 shows uphill distribution and linear scatter

■ DISCUSSION

In our study, we proved that HbA1c level correlated with IOP linear correlation in diabetic group only, mean IOP was higher in diabetic group 17.02 mmHg compared to control group 13.72 mmHg, and was statistically significant, no significant difference regarding age was found, and after including equal numbers of males and females in both groups to avoid bias related to numbers, still there was no significant difference regarding gender, which is the similar to Khalaj et al. [28] (2014) study that showed mean IOP in diabetic group (16.71) was higher compared to nondiabetic group (12.86), and no relation between age, gender and IOP was found.

Another two studies, the Beaver Dam eye study [3] and the Rotter dam study [4], that suggested diabetes mellitus associated with higher intraocular pressure and higher risk of glaucoma.

Another similar result from Matsuoka et al. [29], study conducted on a sample of diabetic patients and nondiabetic controls showed. The mean IOP was 14.0 mmHg in the nondiabetic group and 15.5 mmHg in the diabetic group, and was significantly higher than that in the nondiabetic patients, no significant difference for age or gender was found.

On the other hand, a study by Kaimbo et al. [30] on Congo population showed the relation between diabetes mellitus and intraocular pressure was statistically non-significant, which can result from the relatively low number of diabetic patients included in that study. A study by Quigley et al. [31] on Hispanic population showed that age factor was statistically significant with open angle glaucoma, which differs from our study while diabetes mellitus did not show correlation with intraocular pressure when adjusted for age factor, HbA1c was not used in the study which differs from our study, another study by Voogd et al. [6], showed no association between diabetes mellitus and intraocular pressure, There was variation in the diagnostic criteria for diabetes from our study, such as medication use, fasting, non-fasting or post load blood glucose, which is not included in our study.

In our study, we divided diabetic group according to HbA1c level into well control (group 1 ≤8%) and poor control (group 2 >8%), mean IOP, HbA1c respectively for group 1 (14.55, 7.38%), group 2 (18.28, 9.80%),correlation between IOP, HbA1c was positive and significant only in group 2 (r=0.610, P=0.000), proving that the worse the glycemic control the higher IOP levels, pre diabetic group 3 (<6.5)% mean for IOP, HbA1c respectively was (16.94, 5.78%), there was statistically significant difference in IOP of the three groups, but the correlation between IOP and HbA1c in group 3 was negative, probably to the fact that the sample number of pre diabetic patients was small in that group.

Similar to our result was Oshitari et al. [32], they divided their sample according to HbA1c level into three groups: good control diabetic group (<8%), poor control diabetic group (>8%) pre diabetic group (<6.5%) and there was significant difference in IOP between pre diabetic and poor control groups, t test P value =0.015.

At Boston, according to Hymowitz et al. [33], sample of diabetic patients was divided into two groups, one group with mean HbA1c 8.1, the other 9.0 and IOP range for each group was: 10–14 for the first group, 14.5–22 for the second group, proving that the higher HbA1c levels the more likely the higher IOP levels to be expected.

■ CONCLUSION

Diabetic patients showed high mean intraocular pressure compared to the non-diabetics, with positive correlation between intraocular pressure and the level of HbA1c exist in the Diabetic group, and the strongest correlation was found among the poor control diabetic group.

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