·Investigation·

Distribution of intraocular pressure and its determinants in an Iranian adult population

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Abstract

• AIM: To determine the distribution of intraocular pressure (IOP) and its determinants in an Iranian population.

• METHODS: In a cross-sectional survey, random cluster sampling was conducted from the 40-64 years old population of Shahroud, in the north of Iran. All participants had optometry and ophthalmic exams. IOP was determined using the Goldmann tonometry method and biometric components were measured.

• RESULTS: Of the 6311 people selected for the study, 5190 (82.2%) participated. The mean age of the participants was 50.9±6.2y and 58.7% of them were female. Mean IOP was 12.87±2.27 mm Hg. In this study 0.3% of the participants had an IOP higher than 21 mm Hg. The multiple linear regression model revealed that sex (Coef=-0.30; 95% CI: -0.43 to -0.17), diabetes (Coef=0.43; 95% CI: 0.19 to 0.67), high systolic blood pressure (Coef=0.02; 95% CI: 0.01 to 0.02), high body mass index (BMI) (Coef=0.03; 95% CI: 0.01 to 0.04), higher education (Coef=0.02, 95% CI: 0.01 to 0.04), thicker central corneal thickness (Coef=0.01; 95% CI: 0.01 to 0.02), and myopic shift in spherical equivalent (Coef=-0.14; 95% CI: -0.18 to -0.10) significantly correlated with high IOP.

• CONCLUSION: The IOP in this 40-64 years old population is low overall. In the north of Iran, average IOP is statistically significantly correlated with female sex, diabetes, higher BMI, systolic blood pressure, higher education, thicker cornea, and myopic refractive error.

• KEYWORDS: intraocular pressure; distribution; middle-east; risk factors
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INTRODUCTION

Elevated intraocular pressure (IOP) is one of the major risk factors of glaucoma, and decreased IOP can be associated with certain eye problems such as retinal detachment and uveitis [1-3]. In children, high IOP can lead to corneal enlargement, tears in the Descemet's membrane, and corneal edema [4]. In glaucoma management, percentage reduction in IOP is one of the important indices for different treatment protocols [5-8]. Thus, IOP control mechanisms have extensively been investigated in recent years. These studies show that many systemic, ocular, and even biometric indices may be correlated with IOP [9-16]. One of these important ocular indices is the central corneal thickness which can impact IOP readings; therefore, IOP distribution can differ in different countries in relation to the distribution of central corneal thickness [17-23]. On the other hand, other factors such as systolic blood pressure can influence IOP [24]. Other major risk factors include age, sex, alcohol consumption, smoking, and family history of elevated IOP which have been reported to affect the distribution of IOP[9-14,17,25-29].

In light of the diversity of risk factors, many studies around the world have focused on the distribution of IOP [9-15,17,25-26]. According to these studies, mean IOP is higher in northern

American and European countries compared to east Asian countries [9-17,25-26,30]. Knowledge of the IOP distribution in different regions is essential because in epidemiologic studies, one of the diagnostic criteria for glaucoma is an IOP higher than the 99.5th percentile of the population [1]. Due to ethnic and racial variations in the IOP distribution, study findings of one population cannot be generalized to other populations. Even age-related IOP variations seem to differ among races [9-15,17,25-26,31], just as diurnal IOP fluctuations of an individual can vary[32-33]. The only study describing mean IOP and its determinants in an Iranian population is the Tehran Eye Study [14]. This study showed that the Iranian population, as a sample Middle Eastern population, has lower IOP levels compared to other regions of the world, especially European countries [14]. Nonetheless, more evidence around IOP distribution is needed to confirm these findings regarding Iranian populations. This study was designed to describe the distribution of IOP in a 40 to 64 years old sample population of Shahroud, a city in the north of Iran. In addition, a rather novel aspect of the study is examining the association between IOP and ocular biometric components.

SUBJECTS AND METHODS

This report is part of the first phase of the Shahroud Eye Cohort Study. The first phase was conducted cross-sectionally in 2009 and 2010, and its detailed methodology has been published elsewhere [34]. Here we present a brief summary of the methodology.

The target population of the study was the 40 to 64 years old citizens of Shahroud city, who were chosen through random multistage cluster sampling. Households were systematically selected from the 300 randomly selected clusters, and 20 people were selected in each cluster to be invited for participation in the study.

After enrollment and obtaining written consents from each participant at the clinic site, we collected their demographics, medical history, and ophthalmic history through interview before they underwent complete eye examinations.

Examinations Uncorrected and corrected visual acuity were determined using a logMAR chart, subjective, cycloplegic, and manifest refraction (HEINE BETA 200 retinoscope, HEINE Optotechnik, Germany), autorefraction (Topcon KR 8800 autorefractor, Topcon Corporation, Tokyo, Japan), and lensometry of the participants' eyeglasses. Ophthalmic examinations were done in two stages before and after pupil dilation. Slit lamp biomicroscopy (Haag-Streit BM 900, Haag-Streit, Switzerland) and IOP measurement with Goldmann applanation tonometry were done before cycloplegia. All IOP measurements were done between 9:00 a.m. and 13:40 p.m.; the average time was 11:19 with a standard deviation of 47min.

Grading clinical lens opacities, assessment of vitreous opacities at the slit lamp, and retinoscopy with direct and indirect ophthalmoscopy were done after pupil dilation. Exclusion criteria for this study included use of medication for IOP control and an unreliable IOP reading.

Biometric Examinations These exams were done after testing vision, before ophthalmic examinations and cycloplegic refraction. All participants were examined with the Allegro Biograph (WaveLight AG, Erlangen, Germany) to measure their ocular biometrics.

Statistical Analysis All statistical analyses were done using the STATA software version 12 and IBM SPSS version 22. Considering the correlations of inter-ocular IOP (Pearson correlation=0.766), we used the generalized estimation equation (GEE) method to maintain all data in the analyses. To summarize descriptive variables, we present their mean and 95% confidence intervals (CIs). In calculating standard deviations and 95% CIs, the correlation between contralateral eyes was taken into consideration and all analyses were done using the GEE method. The distribution of IOP is described by different percentiles along with skewness and kurtosis. To explore associations, first we examined them in simple linear regression models using the GEE method, and then they were tested in multiple models to control for confounding factors.

Ethical Issues The Ethics Committee of Shahroud University of Medical Sciences approved the study protocol, which was conducted in accordance with the tenets of the Helsinki Declaration. All participants signed a written informed consent.

RESULTS

In this study, 6311 people were sampled, and 5190 people responded (response rate=82.2%). IOP was not measured in 19 respondents (38 eyes), and eventually, 5171 people (10 342 eyes) were selected for this study. In this group, 30 eyes were excluded from the analyses due to use of medication or an unreliable IOP reading. Eventually, analyses were done using data from 10 312 eyes. The mean age of the participants was 50.9±6.2y (40 to 64y) and 58.7% of them were female.

According to the findings of this study, the mean IOP was 12.87±2.27 (95% CI: 12.79 to 12.95) mm Hg. The Kolmogorov-Smirnov test revealed a significant difference between the IOP distribution and normal (P<0.001). IOP distribution was skewed to the right (skewness=0.949) and had a positive kurtosis (1.5). Mean IOP and 95% CIs by age and sex are presented in Table 1. After adjusting for age, mean IOP was significantly higher in women (P<0.001). IOP significantly increased with age; every year aging increased the IOP by 0.01 mm Hg (P=0.013).

Table 2 displays the mean IOP by other studied variables. Results of the simple generalized linear model for each variable are presented as well. As demonstrated in this table, mean IOP was significantly higher among diabetics. In addition to the significant correlation between higher IOP and systolic blood pressure (Coef =0.019, 95% CI: 0.015 to

Table 1 Mean and 95% CI of IOP by age and sex in Shahroud, Iran

Age groups	Female (*n*=5928)	Male (*n*=4384)	Total (*n*=10312)
40-44 (*n*=1918)	12.78 (12.61-12.94)	12.47 (12.25-12.68)	12.67 (12.54-12.81)
45-49 (*n*=2766)	13.02 (12.88-13.17)	12.72 (12.53-12.91)	12.90 (12.78-13.02)
50-54 (*n*=2557)	13.00 (12.82-13.18)	12.84 (12.64-13.03)	12.93 (12.78-13.08)
55-59 (*n*=1892)	12.96 (12.76-13.16)	12.86 (12.62-13.10)	12.91 (12.75-13.07)
60-64 (*n*=1179)	13.14 (12.87-13.40)	12.66 (12.39-12.92)	12.91 (12.71-13.11)
Total	12.97 (12.87-13.06)	12.73 (12.62-12.84)	12.87 (12.79-12.95)

Table 2 Mean IOP based on some variables and their relationships as seen in simple regression models

Parameters	No. of eyes	Mean (95% CI)	Coefficient (95% CI)	*P*
Diabetic				
Yes	924	13.40 (13.15-13.64)	0.64 (0.40-0.89)	<0.001
No	7809	12.75 (12.67-12.84)	0	
Blood pressure				
Normotensive	2578	12.42 (12.30-12.53)	0	
Prehypertensive	2979	12.78 (12.67-12.89)	0.37 (0.22-0.51)	<0.001
Hypertensive	3176	13.18 (13.05-13.32)	0.77 (0.61-0.93)	<0.001
Education level				
Illiterate	839	12.91 (12.68-13.13)	0	
PrimarySchool	5157	12.77 (12.67-12.87)	-0.13 (-0.36-0.10)	0.256
Middle school	959	12.82 (12.60-13.03)	-0.09 (-0.40-0.22)	0.564
High school	2284	12.99 (12.85-13.13)	0.08 (-0.18-0.34)	0.540
College	1073	13.09 (12.91-13.28)	0.80 (-0.10-0.47)	0.203
Smoking				
Yes	1293	12.48 (12.31-12.65)	-0.45 (-0.62- -0.27)	<0.001
No	9011	12.93 (12.84-13.01)	0	
Refractive errors				
Spherical equivalent	9843		0.90 (0.87-0.93)	<0.001
Emmetropia	3491	12.88 (12.77-12.98)	0	
Myopia	2609	13.13 (12.99-13.26)	0.25 (0.10-0.40)	<0.001
Hyperopi	3743	12.63 (12.52-12.74)	-0.25 (-0.38- -0.12)	<0.001

0.022) and diastolic blood pressure (Coef =0.025, 95% CI: 0.020 to 0.031), people with high blood pressure had the highest IOP readings.

The 25th to 99.5th percentiles by age and sex are presented in Table 3. The 99.5th percentile IOP for the total study sample was 20.0 mm Hg. Also, according to our results, 0.3% of people had an IOP higher than 21 mm Hg.

According to the results of the simple model, IOP was higher in non-smokers, and increased at higher levels of education. The relation between IOP and refractive errors showed an IOP increase with decreases in spherical equivalent (Coef = -0.11, 95% CI: -0.14 to -0.07), such that IOP was highest in myopes and lowest among hyperopic participants, and IOPs in these two groups were significantly different from that in emmetropes.

Table 4 summarizes the IOP relation to biometric components. As demonstrated, the axial length of the eye, central corneal thickness, and pupil diameter significantly correlated with IOP in the simple model. To control for the concurrent effect of biometric parameters and confounding factors, IOP relationships with ocular biometrics were studied in a multiple model, results of which are presented in Table 4. In this model, axial length, central corneal thickness, pupil diameter, and minimum keratometry significantly correlated with IOP.

Table 3 Distribution indices of IOP and their percentiles by age and sex

Parameters	Percentiles				
	25th	50th	95th	97.5th	99.5th
Age (a)					
40-44	11	12	16	18	20
45-49	11	12	17	18	20
50-54	11	12	17	19	20
55-59	11	12	17	18	22
60-64	11	12	17	18.5	20
Sex					
F	11	12	17	18	20
M	11	12	17	18	20
Total	11	12	17	18	20

Table 4 Relationship between IOP and ocular biometrics according to simple regression and multiple generalized linear models

Ocular biometric component	Simple regression model		Multiple regression model	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
AL (mm)	0.10 (0.03-0.17)	0.003	0.21 (0.13-0.29)	<0.001
CCT (μm)	0.01 (0.01-0.01)	<0.001	0.01 (0.01-0.02)	<0.001
ACD (mm)	0.11 (-0.06-0.27)	0.213	-	-
LT (mm)	0.00 (-0.20-0.20)	0.988	-	-
WTW (mm)	-0.08 (-0.18-0.03)	0.156	-	-
K1 (D)	0.03 (0.00-0.07)	0.079	0.14 (0.1-0.19)	<0.001
K2 (D)	0.03 (-0.01-0.06)	0.120	-	-
PD (mm)	0.21 (0.13-0.29)	<0.001	0.21 (0.13-0.28)	<0.001

AL: Axial length; CCT: Central corneal thickness; ACD: Anterior chamber depth; LT: Lens thickness; WTW: White to white corneal diameter; K1: Minimum keratometry; K2: Maximum keratometry; PD: Pupil diameter; CI: Confidence interval.

We studied the relationship between IOP and other variables in a multiple generalized linear model. In this model, we entered age, sex, education, spherical equivalent, systolic blood pressure, diastolic blood pressure, BMI, diabetes, smoking and biometric components and the results are presented in Table 5. According to this model, female sex, higher levels of education, being diabetic, high systolic blood pressure, high BMI, thicker central cornea, and lower spherical equivalent were statistically significantly correlated with higher IOP.

Table 5 Relationship between IOP and studied variables based on a multiple generalized linear model

Variables	Coefficient (95%CI)	*P*
Gender (M/F)	-0.30 (-0.43 to -0.17)	<0.001
Education (a)	0.02 (0.01 to 0.04)	<0.001
Diabetic (Y/N)	0.43 (0.19 to 0.67)	<0.001
Systolic blood pressure (mm Hg)	0.02 (0.01 to 0.02)	<0.001
Body mass index	0.03 (0.01 to 0.04)	<0.001
Central corneal thickness (μm)	0.01 (0.01 to 0.02)	<0.001
Spherical equivalence (D)	-0.14 (-0.18 to -0.10)	<0.001

CI: Confidence interval.

DISCUSSION

In this report we presented a detailed study of IOP distribution in a 40 to 64 years old Iranian population. Additionally, we studied IOP relations with biometrics which have been discussed in very few studies by Broman *et al*[35], Yang *et al* [36], and Tomoyose *et al* [37]. The strong points of the study include its large sample size, which also compensates for the fact that we measured IOP only once and minimizes intra-individual measurement errors that may occur as a result of diurnal fluctuations.

Mean IOP in the present study was 12.87±2.27 mm Hg, and as demonstrated, the histogram was skewed towards higher readings. Results of some other studies are presented in Table 6. As demonstrated in this table, mean IOP shows a wide range from 12.8 to 18.7 mm Hg in population-based studies. This wide range is partly due to the age structure of the studies. Comparison of over 40 years old age groups shows that the highest IOP belongs to the Barbados Eye Study [26], and the IOP in our study was lower than all other studies, even the Tehran Eye Study (Table 6). This finding may be difficult to explain. One reason may be the limited range and not including those over 64 years of age. Another potential factor could be the variety of IOP measurement devices. In addition, since IOP correlates with many factors such as biometrics, family history of glaucoma, age, sex, *etc.*[9-14,17,25-29], different distributions of these factors in different geographic areas can be another reason for the observed differences in

Table 6 Results of other studies concerning IOP

Authors	Country	Age group (a)	$\bar{x} \pm s$
Tomoyose *et al*[37]	Japan	≥40	15.1±3.1
Wong *et al*[24]	Korea	40-99	13.5±2.7
Foster *et al*[40]	British	48 to 91	16.0±3.68
Zheng *et al*[25]	China	8-16	14.2±2.3
Leske *et al*[26]	USA	40-84	Black: 18.7±5.2 Mixed: 18.2±3.8 White: 16.5±3.0
Hoehn *et al*[9]	Germany	35 to 74	14.0±2.6
Sakalar *et al*[17]	Turkey	5-18	14.15±2.8
Landers *et al*[11]	Australia	≥20	12.8±3.2
Hashemi *et al*[14]	Tehran	≥40	15.1±2.9
Giuffrè *et al*[41]	Italy	31-40	15.1±3.7

IOP distribution. For example, BMI correlates directly with IOP [38-39].This index is relatively high in European countries and low in east Asian countries. As for IOP, again we see higher averages in European countries and lower ones in east Asian countries.

As demonstrated, IOP distribution was skewed to the right. A similar observation was made in some other studies [14,42-43]. Since younger people have IOP in the normal range, distribution skewness is not expected in these age groups. But since glaucoma, especially open angle glaucoma, increases with age, it is not unexpected to see a higher IOP which is the major risk factor [44]. Thus, the distribution being skewed

to the right in this age group is due to the high IOP in some people.

In this study, the IOP was higher than 21 mm Hg in 0.3% of the studied population; other studies have reported higher percentages. Since the average IOP in our study was lower than other studies (Table 6), the cutoff point must be determined based on percentiles calculated from this study.

The IOP was higher in the women in our study. The Tehran Eye Study [14] found no significant IOP difference between men and women. Results of other studies regarding the relationship between IOP and sex are inconclusive. In agreement with our results, studies in Korea have reported higher IOP in women [10]. On the contrary, IOP was higher in men in studies in Italy [31] and Barbados [26]. Results regarding open angle glaucoma are conflicting as well. For example, inter-gender differences in the prevalence of glaucoma were not statistically significant in Barbados [45] and Beaver Dam[46] studies, but Melbourne[47] and Rotterdam[48] studies found men to be at higher risk of glaucoma. In a study by Pasquale and Kang[49], oral contraceptives were found to be associated with a higher incidence of open angle glaucoma as an effect of circulating estrogens. Some IOP variations in women may be caused by changes in estrogen, and further studies in this area seem necessary.

As demonstrated, IOP increased with age in the simple and adjusted models; nonetheless, there was no correlation after adjusting for other variables. The relationship between age and IOP has been reported differently in previous studies. In Tehran [14], Italy [31], Beaver Dam [50], Barbados [26], and Framingham[51] studies, IOP increased with age, while results in east Asian countries have been different. For example, in five studies in Japan [52-56] and South Korea [57], IOP decreased with age. In another Asian population, Wong *et al* [24] found that IOP increased up to the age of 60y and decreased thereafter. According to a study in China, IOP increased up to the age of 64 years and decreased thereafter[58]. In the Blue Mountains Eye Study [28], IOP increased with age, but the relationship was reversed after adjusting for systolic blood pressure, and eventually, after adjusting for diabetes, family history of glaucoma, and myopia, the model revealed there was no correlation between IOP and age. The study on the population of Karachi found an age-related increase in IOP until age 60, a plateau between 60 and 70 years of age, followed by IOP increase thereafter [59]. IOP changes have been investigated in cohort studies as well. For example, in the Barbados study, a modest increase of 0.4 mm Hg was observed after 9y. In a longitudinal study in Sweden, the IOP change over a 21y period was 0.05 mm Hg. In another longitudinal study in Japan, a slight IOP increase was observed with aging. However, the longitudinal study in Beijing demonstrated an IOP decrease of 1.25 mm Hg over a 5y period. The relationship between age and IOP seem to be affected by other age-related risk factors such as blood pressure, diabetes, and even obesity, because, like us, most studies that adjusted for these variables did not find any age-related IOP increase, or even observed and age-related decrease in IOP.

Results of our study indicated a direct relationship between IOP and systolic blood pressure in all regression models. This is in agreement with results of several population-based and clinical studies[24,37,51,54,60-65]. However, unlike us, few studies[61,66] have demonstrated a relationship between IOP and diastolic pressure.

Diabetes was another risk factor for increased IOP which was observed in the final multiple model of our study. This relationship has been described from univariable models as well [9,67]. Also, studies in Japan [37,68], the Los Angeles Latino Eye Study [63], and the Tehran Eye Study [14] observed this relationship after adjusting for other variables such as age. The Barbados Eye Studies [69] and the Beaver Dam Study[64] found greater IOP changes over time among diabetics. The role of diabetes in the development of open angle glaucoma has been investigated in many studies, and has been demonstrated in a Meta-analysis as well [70]. However, some population-based studies with large sample sizes, such as Baltimore[71], Beijing[72], south India[73], Los Angeles Latino[74], and Barbados[75] studies have reported no relationship between diabetes and glaucoma.

BMI was another risk factor for increased IOP which showed a significant correlation in the simple and multiple models. Each unit increase in BMI was associated with 3% increase in IOP. The positive relation between BMI and IOP have been reported by investigators from Korea [9,76], Japan[53,55,60,69], Taiwan (China) [61], and China [72,77]. Some studies have examined the relationship between IOP and the BMI in children, but their results are inconclusive[78-80].

Our findings indicated that IOP was highest among myopes and lowest among hyperopic participants. As demonstrated, this relationship existed after adjusting for axial length and other variables as well. A higher IOP in myopes has been observed in previous studies [58,68,79-82], and myopia has been reported as a glaucoma risk factor [82-85]. There are studies that show a temporary relationship between higher myopia and IOP [86-87]. A simple regression model in our study found a direct and significant relationship between IOP and axial length which was not observed in the final model. The relationship between IOP and myopia observed in the final model might be due to the relationship between IOP and axial length, and refraction in cases with higher IOP readings shows a shift towards myopia through a longer axial length. A few studies have shown the association between IOP and longer axial lengths [37]. In children however, the relationship has been negated [88]. It is difficult to give a biologic

explanation for the IOP relationship with axial length and further studies are needed to clarify this issue.

An interesting finding of our study was the direct relationship between IOP and education which has been confirmed in some other studies as well. Since near work, especially reading, is more common among more educated people, this relationship could be an effect of near work. Accommodation tends to be stronger during near work. Increased accommodation is associated with increased axial length and lens thickness which can raise the IOP.

CONCLUSION

Mean IOP in the 40-64 years old population of Shahroud was lower than averages reported in most other studies. This is of special importance in the diagnosis of glaucoma in Iranian populations, and further evaluations in this population are needed to define cutoff points for identifying cases at risk of glaucoma. As observed in other studies, diabetes, blood pressure, and obesity were among risk factors that demonstrated a correlation with IOP. These risk factors should be noted in patient check-ups and in identifying cases at risk of glaucoma.

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