Relationship between hematocrit levels and intraocular pressure in men and women
A population-based cross-sectional study

Eytan Cohen, MDa,b,e, Michal Kramer, MDc,e, Tzippy Shochat, MScd, Elad Goldberg, MDb,e, Ilan Krause, MDa,e

Abstract
To assess a possible relationship between hematocrit level and intraocular pressure (IOP) in both men and women.

Data were collected from medical records of individuals examined at a screening center in Israel between the years 2000 and 2013. Hematocrit levels were categorized as low, normal, and high and by sex; IOP values were categorized as < 18 mmHg and ≥18 mmHg.

Cross-sectional analysis was performed on 18,424 subjects of mean (standard deviation) age 46 (10) years (68% male). Normal-range hematocrit for men was 42% to 52% and 37% to 47% for women. In men, mean [95% confidence interval (CI)] IOP values by hematocrit level were as follows: below-normal hematocrit, 13.3 mmHg (13.2–13.3), normal hematocrit, 13.5 mmHg (13.4–13.5), above-normal hematocrit, 14.3 mmHg (13.5–15.2) (P < .001). Corresponding values in women were 12.9 mmHg (12.8–13.0), 13.0 mmHg (13.0–13.1), and 14.2 mmHg (12.9–15.6) (P = .014). The difference remained significant for men (P < .001) after adjustment for age, hypertension, diabetes, and body mass index. Men (but not women) with a low hematocrit were found to have a significantly lower odds ratio (95% CI) of having IOP ≥18 mmHg than men with normal hematocrit: nonadjusted model, 0.761 (0.631–0.919); adjusted model, 0.771 (0.638–0.932) (P < .01).

It is possible that a raised hematocrit level may also contribute to an elevated IOP in men in addition to the classic risk factors.

Abbreviations: AGIS = Advanced Glaucoma Intervention Study, ANOVA = analysis of variance, BMI = body mass index, CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtrations rate, HDL = high density lipoprotein, IOP = intraocular pressure, LDL = low density lipoprotein, NS = non significant, OR = odds ratio, SD = standard deviation, SE = standard error, TSH = thyroid stimulation hormone.

Keywords: body mass index, diabetes mellitus, glaucoma, hematocrit, hypertension, intraocular pressure

1. Introduction
Glaucoma is the leading cause of blindness worldwide after cataracts.[1] It is the main reason for blindness among African Americans.[2,3] In addition to older age, black race/ethnicity and a family history of glaucoma, elevated intraocular pressure (IOP) is a major risk factor for the development of open-angle glaucoma[4,5] and it has been associated with progression of open-angle glaucoma. Lowering IOP is thus the major focus of glaucoma treatment.[6–8] Factors that affect IOP per se include older age, high blood pressure[9] elevated glucose levels[10] and elevated body mass index (BMI).[11]

Several epidemiological studies have investigated the correlation between IOP and clinical and biochemistry tests. They found a weak correlation between IOP and hematocrit levels.[12–14] However, the studies did not account for sex differences in normal hematocrit levels, nor did they compare IOP in subjects with low or high hematocrit levels with those with a normal hematocrit level.

The aim of the current study, carried out on nonhospitalized men and women was to evaluate IOP measurements in relation to hematocrit levels. In addition, we calculated the risk of having an IOP of ≥18 mmHg in subjects with high or low hematocrit levels.

2. Materials and methods

2.1. Study population
The study population consisted of a cross-sectional sample of men and (nonpregnant) women aged 20 to 80 years referred by their employers for routine medical screening at a tertiary medical center in Israel between 2000 and 2013. None of the subjects was hospitalized at the time. Screening consisted of a thorough medical history and a complete physical examination along with a broad series of blood and urine tests, a chest x-ray, an electrocardiogram, an exercise stress test, a respiratory function test, and a full ophthalmology examination. For the purpose of this study, we used the data from each subject’s most recent visit,
as they may return for an annual visit. Subjects who had glaucoma or were scheduled for surgery for glaucoma were excluded from the study, as they were receiving IOP-lowering medication which might influence the effect of hematocrit on IOP.

All ophthalmology examinations were performed by an experienced ophthalmologist. IOP measurements using Goldmann applanation tonometry with fluorescein staining were measured in both eyes, with the patient in the sitting position, between 8:00 AM and 11:00 AM. All IOP measurements were performed using the same tonometer and were usually carried out by the same physician. For the study assessment we selected the right eye IOP measurements. We further categorized IOP as \( \geq 18 \) mmHg or \( \geq 18 \) mmHg, according to the results of the Advanced Glaucoma Intervention Study 7 (AGIS).

Serum glucose levels were measured after an overnight 12-hour fast. Diabetes mellitus was defined as serum glucose levels \( \geq 126 \) mg/dL or a known diagnosis of diabetes mellitus. Hypertension was defined as systolic blood pressure \( >140 \) mmHg and/or diastolic blood pressure \( >90 \) mmHg. Subjects in this group were identified as those with self-reported hypertension treated mostly by antihypertensive medications. Data on smoking habits and alcohol consumption were collected from direct questioning on the day of examination at the screening center.

A computer program was created to transfer all data, from each visit, into a spreadsheet Excel file. Statistical analysis was performed on this file.

For purpose of analysis, patients were divided into 3 groups according to hematocrit level (low, normal, and high), separately for men and women, and mean IOP was calculated for each.

The study was approved by the Helsinki Ethics Committee of Rabin Medical Center.

### 2.2. Statistical analysis

Baseline characteristics were compared between men and women using Student's t test for continuous variables and \( \chi^2 \) test for categorical variables. Subjects were divided into 3 groups by hematocrit levels: normal (reference group), low and high, and compared for mean IOP [95% confidence interval (CI)] using multivariate analysis of variance (ANOVA) with Tukey's adjustment.

The odds ratios (ORs) and 95% CI for having an IOP of \( \geq 18 \) mmHg were calculated by hematocrit level using logistic regression. Pearson correlation index was applied to assess the relationship between hematocrit level and IOP.

Univariate analyses were performed in Model 1. Model 2 was adjusted for age, and Model 3 was adjusted for age, hypertension, diabetes mellitus, and BMI. All analyses were performed using SAS v. 9.4. Statistical significance was set as a \( P < 0.05 \).

### 3. Results

#### 3.1. Baseline characteristics

From 2000 to 2013, 18,424 subjects underwent screening at our medical center. Their clinical characteristics are presented in Table 1. Mean [standard deviation (SD)] age of the sample was 46.0 (10) years; 68% were male and 32% female. Comparison of men and women for background characteristics yielded no statistically significant differences in mean age (\( P = 0.367 \)) or percentage of smokers (\( P = 0.174 \)). Men had significantly higher rates of impaired fasting glucose, diabetes mellitus, hypertension, and alcohol consumption, and significantly higher mean values of BMI, low density lipoprotein cholesterol, and triglycerides (\( P < 0.001 \) for all). Women had significantly higher mean values of estimated glomerular filtration rate, serum thyroid stimulating hormone, and high density lipoprotein cholesterol (\( P < 0.001 \) for all).

#### 3.2. Mean IOP by hematocrit level

The normal-range hematocrit level in men was 42% to 52%, with low levels defined as \( < 42% \) and high levels, as \( > 52% \). The normal-range hematocrit level in women was 37% to 47%, with low levels defined as \( < 37% \), and high levels, as \( > 47% \). Mean IOP (SD) measured 13.4 mmHg (2.5) in men and 13.0 mmHg (2.2) in women; this difference was statistically significant (\( P < 0.001 \)).

Mean (95% CI) IOP in subjects with low, normal, and high hematocrit levels were also found to be significantly different. These were found to be 13.3 (13.2–13.3), 13.5 (13.4–13.5), and 14.3 (13.5–15.2) mmHg for men, \( P < 0.001 \) and 12.9 (12.8–13.0), 13.0 (13.0–13.1), and 14.2 (12.9–15.6) mmHg for women, \( P < 0.01 \), respectively. After adjusting for age, hypertension, diabetes mellitus, and BMI the differences in IOP for different hematocrit levels remained significant for men but not for women (Table 2). Figure 1 represents the above data as means ± standard error.

#### 3.3. Risk of IOP \( \geq 18 \) mmHg by hematocrit level

Table 3 shows the ORs (95% CIs) of having IOP \( \geq 18 \) mmHg in subjects with high or low hematocrit levels compared with subjects with normal hematocrit levels. In male subjects with a low hematocrit level, the OR (95% CI) of having IOP \( \geq 18 \) mmHg was 0.761 (0.631–0.919) in the unadjusted model, 0.757 (0.626–0.914) when the model was adjusted for age, and 0.771 (0.638–0.932) when the model was adjusted for age, hypertension, diabetes mellitus, and BMI (\( P < 0.01 \)). The risk in the women was not statistically significant (Table 3).

#### 3.4. Correlation of hematocrit levels and IOP

Pearson correlation analysis of the relationship between hematocrit and IOP level yielded \( r = 0.047 \) for men and
Male subjects with glaucoma have both higher plasma viscosity levels and higher IOP levels. \[11\] The current study of the potential relationship between BMI and IOP, with obese people having higher hematocrit levels and IOP, although as a whole, the men with low or high hematocrit levels had significantly lower or higher IOP levels, respectively, compared with men with normal hematocrit levels; this was even after adjusting for age, hypertension, diabetes mellitus, and BMI. \[12-14\] However, these results were limited by a failure to distinguish between men and women, who have different normal-range hematocrit levels. Nor did the data compare IOP between groups of subjects with low or high hematocrit levels and those with normal hematocrit levels. In the current study, which sought to take these factors into account, we only found a very weak direct correlation between hematocrit levels and IOP, which was even after adjusting for age, hypertension, diabetes mellitus, and BMI.

The main strength of this study is the inclusion of a large cohort (18,424 men and women) with complete datasets and a broad age range, largely representative of a western population. However, mental systems. This effect on muscle tone and vascular resistance might be explained by the generally lower hematocrit levels found in female subjects with glaucoma. Indeed, Vojnikovic\[17\] found that treatment with a blood hyper viscosity-reducing drug (Doxium) lowered elevated IOP in patients with diabetic retinopathy and patients with glaucoma.

4. Discussion

A large body of literature has described the association between elevated IOP and the development and progression of open-angle glaucoma.\[6-8\] In a recent study, our group found a significant relationship between BMI and IOP, with obese people having higher IOP levels.\[11\] The current study of the potential relationship between high hematocrit levels and IOP was prompted by previous findings of a correlation between plasma viscosity and glaucoma. Klaver et al.\[16\] reported that subjects with glaucoma have both higher plasma viscosity levels and higher hematocrit levels than controls. Indeed, Vojnikovic\[17\] found that treatment with a blood hyper viscosity-reducing drug (Doxium) lowered elevated IOP in patients with diabetic retinopathy and patients with glaucoma.

Several epidemiological studies of the relationship between IOP and various clinical and biochemical parameters reported a weak correlation with hematocrit levels.\[12-14\] However, these results were limited by a failure to distinguish between men and women, who have different normal-range hematocrit levels. Nor did the data compare IOP between groups of subjects with low or high hematocrit levels and those with normal hematocrit levels. In the current study, which sought to take these factors into account, we only found a very weak direct correlation between hematocrit levels and IOP, which was even after adjusting for age, hypertension, diabetes mellitus, and BMI.

The lack of a significant difference in IOP between men and women with high hematocrit levels can probably be attributed to the relatively small number of subjects with a high hematocrit level (n=40). Studies in large groups of patients with polycythemia vera are needed to determine their risk of high IOP.

The sex difference in the current study was very clear. It may be explained by the generally lower hematocrit levels found in women compared with men. Although theoretically smokers may have increased hematocrit levels, no significant difference in smoking habits between the male and female subjects was found in our cohort. It is possible that the difference in favor of women may be related to their higher estrogen levels. Studies have shown that estrogen may lower ocular pressure by influencing the aqueous production in the eye and outflow systems. This effect on muscle tone and vascular resistance might be explained by increased activity of endothelial based nitric oxide synthase.\[18\]

Table 2

| Table 2 | Relationship of hematocrit level with IOP in men and women. |
| --- | --- |
| Hematocrit groups by sex | Hematocrit level (%) | No. of subjects | Mean IOP (mmHg) (95% CI) |
| Male | Low | <42 | 2943 | 13.3 (13.2–13.3) |
| | Normal | 42–52 | 9631 | 13.5 (13.4–13.5) |
| | High | >52 | 40 | 14.2 (13.5–15.2) |
| P | 0.001 |
| Women | Low | <37 | 1114 | 12.9 (12.8–13.0) |
| | Normal | 37–47 | 4677 | 13.0 (13.0–13.1) |
| | High | >47 | 19 | 14.2 (12.9–15.6) |
| P | 0.014 |

| Table 3 | Odds of having IOP ≥18 mmHg in subjects with high/low hematocrit compared with subjects with normal hematocrit. |
| --- | --- |
| Logistic regression models by sex | Low hematocrit | High hematocrit |
| Male subjects | Model 1 | 0.761 (0.631–0.919) | 2.163 (0.845–5.459) |
| | Model 2 | 0.757 (0.626–0.914) | 1.899 (0.738–4.877) |
| | Model 3 | 0.771 (0.638–0.932) | 1.927 (0.746–4.981) |
| Female subjects | Model 1 | 0.710 (0.470–1.074) | 1.589 (0.211–11.977) |
| | Model 2 | 0.828 (0.546–1.258) | 1.150 (0.151–8.756) |
| | Model 3 | 0.849 (0.558–1.290) | 1.118 (0.144–686) |

*For unadjusted (Model 1), adjusted for age (Model 2) and adjusted for age, hypertension, diabetes, and BMI (Model 3). \[12\] Unadjusted only. BMI = body mass index, CI = confidence interval, IOP = intraocular pressure.

Figure 1. Mean (SE) intraocular pressure in men and women with low, normal and high hematocrit levels. Comparison of mean intraocular pressure of subjects with low or high hematocrit levels to mean intraocular pressure of subjects with normal hematocrit levels. \[P < .001 for men. \[P = .014 for women. SE = standard error. \]
as the study group was drawn from a selected population attending an examination center, rather than a population sample, the findings may not be generalizable. Furthermore, the cross-sectional design precludes conclusions regarding causality.

In summary, this study indicates that apart from the classic risk factors for increased IOP, including older age, diabetes mellitus, hypertension and BMI, IOP may also be influenced by hematocrit level in men.

References

[1] Kingman S. Glaucoma is second leading cause of blindness globally. Bull World Health Organ 2004;82:887–8.
[2] Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121:2081–90.
[3] Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. N Engl J Med 1991;325:1412–7.
[4] Kwon YH, Fingert JH, Kuehn MH, et al. Primary open-angle glaucoma. N Engl J Med 2009;360:1113–24.
[5] Cudovska MA, Ramdas WD, Wolfs RC, et al. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology 2010;117:1705–12.
[6] Ekstrom C. Risk factors for incident open-angle glaucoma: a population-based 20-year follow-up study. Acta Ophthalmol 2012;90:316–21.
[7] Nemesure B, Honkanen R, Hennis A, et al. Incident open-angle glaucoma and intraocular pressure. Ophthalmology 2007;114:1810–5.
[8] Martínez-Bello C, Chauhan BC, Nicolela MT, et al. Intraocular pressure and progression of glaucomatous visual field loss. Am J Ophthalmol 2000;129:302–8.
[9] Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. Arch Ophthalmol 1997;115:1572–6.
[10] Zhao D, Cho J, Kim MH, et al. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. Ophthalmology 2013;122:72–8.
[11] Cohen E, Kramer M, Shochat T, et al. Relationship between body mass index and intraocular pressure in men and women: a population-based study. J Glaucoma 2016;25:e509–13.
[12] Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Eye Study. Invest Ophthalmol Vis Sci 1992;33:2224–8.
[13] Nakano T, Tatemichi M, Miura Y, et al. Long-term physiologic changes of intraocular pressure: a 10-year longitudinal analysis in young and middle-aged Japanese men. Ophthalmology 2005;112:609–16.
[14] Kim YK, Choi HJ, Jeong JW, et al. Five-year incidence of primary open-angle glaucoma and rate of progression in health center-based Korean population: the Gangnam Eye Study. PLoS One 2014;9:e114058.
[15] The Advanced Glaucoma Intervention Study (AGIS): The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000;130:429–40.
[16] Kla ver JH, Greve EL, Goslinga H, et al. Blood and plasma viscosity measurements in patients with glaucoma. Br J Ophthalmol 1985;69:765–70.
[17] Vojnikovic B. Dextium (calcium dobesilate) reduces blood hyperviscosity and lowers elevated intraocular pressure in patients with diabetic retinopathy and glaucoma. Ophthalmic Res 1991;23:12–20.
[18] Vajaranant TS, Pasquale LR. Estrogen deficiency accelerates aging of the optic nerve. Menopause 2012;19:942–7.