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Intraocular Pressure and Corneal and Macular Thickness in Men: A Pilot Study on Hormonal, Metabolic, and Physical Effects

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Abstract: (1) Background/Objectives: This pilot study aims to address the research gap on the interplay between ocular and systemic parameters as well as sex hormones in men. (2) Methods: We measured intraocular pressure (IOP), central corneal thickness (CCT), and macular thickness (CMT) in nine healthy male volunteers. These measures, along with blood glucose; blood pressure; and sex steroid hormones (testosterone, estrogen, and progesterone), were measured twice for each subject. Linear regression was used to determine the individual effects of these measures as well as self-reported age, height, and weight. (3) Results: Height, weight, systolic blood pressure, blood glucose, and estrogen significantly predicted IOP and CMT. CCT models were more limited, with systolic blood pressure and estrogen as the most significant predictors. (4) Conclusions: Our findings suggest that height, weight, blood pressure, and estrogen levels have the most substantial impact on ocular measurements. Testosterone levels were strongly associated with systemic health markers, a common result in the literature. However, ours appears to be the first study demonstrating estrogen's effects on ocular structure or physiology in men. As many of our comparisons were statistically underpowered, future research with larger populations is needed to confirm these relationships and elucidate underlying mechanisms.

Keywords: intraocular pressure; corneal thickness; macular thickness; males; salivary hormones; estrogen; progesterone; testosterone

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1. Introduction

The measurement of ocular parameters provides essential information for maintaining ocular health and diagnosing ocular conditions. One of the most critical parameters is intraocular pressure (IOP), as elevated IOP is a major risk factor for glaucoma, a condition that can lead to blindness [1,2]. Several intrinsic factors, such as age, sex, and genetic modifications, are known to affect IOP [3,4], while other factors, including stress, obesity, posture, exercise, and metabolic and hormonal alterations, also play a role [5,6].

Central corneal thickness (CCT) can also contribute to variations in IOP measurements, as thinner or thicker corneas can affect the accuracy of IOP readings, particularly when non-contact tonometry is used [7]. Additionally, an increased prevalence of ocular hypertension has been observed in individuals with thicker corneas [8]. Another important parameter to consider is central macular thickness (CMT), as significant increases in IOP have been associated with a decrease in central macular thickness [9], which directly impacts central vision.

Beyond ocular factors, systemic variables, such as blood pressure, blood glucose, and hormone levels, are also known to influence ocular physiology [10,11]. This effect is thought to be mediated by changes in ocular blood flow, collagen properties, or fluid regulation [12,13].

Although numerous studies have explored the relationship between systemic health and ocular disease in men [14,15], there is a noticeable gap in research specifically addressing the interplay between ocular and systemic parameters. Additionally, while there have been investigations into the effects of testosterone on systemic and ocular parameters as well as visual function in males [16,17], there have been far fewer investigations of estrogen or progesterone effects. For example, only one study has addressed the relationship between estrogen and IOP in men [18]. To our knowledge, this is the first study that addresses the relationship between central macular thickness and sex hormones in men, as well as progesterone and ocular parameters in men. With the increasing transgender population receiving sex hormones, the evaluation of these relationships has gained more relevance.

In a previous descriptive analysis of IOP, CCT, and CMT, we found robust differences between oral hormonal contraceptive users and cycling women [19]. We also found differences between women and a small sample of men, most significantly when comparing central macular thickness. However, those differences were most notable between men and cycling women. We also found trends for higher IOP in men, a result similar to a large-scale study in Korean men and women [5]. Our IOP trend became significant when comparing men with women in the low progesterone phase of their menstrual cycles. It is then tempting to attribute observed differences to sex hormones, but we know of no study that has examined the pooled effects of estrogen, progesterone, and testosterone on IOP, CCT, or CMT.

This pilot study aims to address these research gaps by evaluating the impact of these hormones as well as physical characteristics (age, height, and weight) and metabolic factors (blood pressure and blood glucose level) on ocular parameters in a small sample of men (N = 9). The goal is to improve the current understanding and assessment of sex-driven differences in ocular health.

2. Materials and Methods

2.1. Participants

Data from nine men were considered in this pilot study. Exclusion criteria included a clinical history of diabetes mellitus (DM), hypertension (HTN), thyroid disease, current oral or topical ophthalmic anti-inflammatory medication use, a history of glaucoma, and refractive surgery. Participants all identified as cis male and ranged in age from 23 to 50 (mean = 30.0 and S.D. = 8.05) years. There was a modicum of ethnic diversity, with subjects identifying as either white, non-Hispanic (N = 5); Asian (N = 2); or white, Hispanic (N = 2). The study protocol was approved by the institutional review board at the University of the Incarnate Word (UIW #14-05-002), and informed consent was obtained from all subjects.

2.2. Scheduling and Procedure

Participants were scheduled for two sessions two weeks apart. To minimize the confounding diurnal effects on intraocular pressure [20–22], we conducted all procedures between 7:00 and 9:00 a.m. Each session began for all participants with blood pressure (BP) and fasting blood glucose level (BGL) measurements. Height and weight were recorded from participants' self-reports.

2.3. Ocular Parameter Measurements

Intraocular pressure (IOP) was measured using the iCare® IC100 rebound tonometer (Icare USA, Inc., Raleigh, NC, USA), which calculates a mean measurement based on six readings, for both eyes during each testing session. Central corneal thickness (CCT) was assessed using the PachPen® pachymeter (Accutome, Inc., Malvern, PA, USA). This device calculates the mean CCT by averaging ten measurements and retaining only the perpendicular readings. We recorded mean CCT values for each eye during each test session. Additionally, central macular thickness (CMT) was measured using the Zeiss Cirrus TM 4000 spectral domain optical coherence tomography (Zeiss AG, Oberkochen, Germany) with a 512×128 macular scan pattern. Reliable scans (signal strength $\geq 9/10$) were saved for each eye based on subject number and session. The central subfield thickness was noted as central macular or foveal thickness (CMT) for each eye.

2.4. Salivary Hormone Analysis

Saliva specimens were collected with Saliva Collection Aid (Salimetrics, Inc., State College, PA, USA) into a cryo-vial and stored at $-20\ ^{\circ}C$. Per the manufacturer, samples may be store at this temperature for up to six months, and all of ours were assayed within three months for estrogen (EST), progesterone (PGT), and testosterone (T) using commercially available enzyme immunoassay (EIA) kits (Salimetrics, Inc., State College, PA, USA). Salimetrics salivary kit catalog numbers were as follows: Testosterone (1-2402), Estradiol (1-3702), and Progesterone (1-1502). Samples visibly contaminated with blood were discarded. Microtiter plates coated with horseradish peroxidase-labelled rabbit antibodies to EST, PGT, and T were incubated with saliva samples (25, 50, and 100 mL, respectively, depending on the hormone assessed) for 1 h at room temperature. After incubation, unbound components were washed away, and bound hormones were measured by the reaction of the peroxidase enzyme on the substrate tetramethylbenzidine (TMB). This reaction produces a blue color. A yellow color is formed after stopping the reaction using 2-molar sulfuric acid. Optical density was read on a plate reader at 450 nm. The amount of hormones peroxidase detected was inversely proportional to the amount of hormone present [23]. All assays were studied in duplicate.

2.5. Data Analysis

We first compared all variables to normal distributions using the Kolmogorov–Smirnov goodness-of-fit test. Diastolic blood pressure (DBP), IOP, CCT, T, and EST were normally distributed. Age, height, weight, BGL, systolic blood pressure (SBP), CMT, and PGT were not normally distributed. CMT inter-eye and between-session differences were then compared via non-parametric Mann–Whitney tests. IOP and CCT differences were compared via paired *t*-tests. Since robust linear regression only depends on a linear pre-modeled relationship and whether post-modeled residuals vary with the magnitude of the predicted outcomes (i.e., error homoskedasticity), inferences are preserved even if outliers are present, and predictors are not normally distributed. We then stacked the fixed factors (inter-eye and between-session differences) in a univariate analysis of variance (ANOVA) using robust standard errors for the nested model regression equations for each primary outcome—IOP, CCT, and CMT.

The regression models for IOP, CCT, and CMT each contained 36 total observation equations (9 participants $\times$ 2 sessions $\times$ 2 eyes). We analyzed the linear model for IOP with the following parameters: physical (age, height, and weight); metabolic (BGL, systolic BP, and diastolic BP); ocular (CCT and CMT); and hormone levels (EST, PGT, and T). All model predictors were treated as covariates, and model error variance heteroskedasticity

was evaluated via Breusch–Pagan modified tests. CCT and CMT were modeled identically, except for using IOP and CMT or IOP and CCT, respectively, as ocular predictors.

Relationships between physical characteristics, metabolic markers, ocular parameters, and hormone levels were also examined by bivariate correlation analyses. We used IBM SPSS Statistics (Version 29) for all regression and correlation analyses. Lastly, we performed post hoc power analyses for the regression and correlation analyses.

3. Results

3.1. Descriptive Results

Descriptive results for all outcome measures for all subjects are shown in Table 1. There were no IOP differences between the right and left eyes (Mean difference [MD] = 0.28 mmHg; 95% CI: [−2.63, 3.19]; and $p = 0.847$) or between sessions (Mean difference [MD] = −0.50 mmHg; 95% CI: [−3.41, 2.41]; and $p = 0.729$). There were also no CCT differences between right and left eyes (Mean difference [MD] = −4.61 μ; 95% CI: [−34.09, 24.87]; and $p = 0.753$) nor between sessions (MD = 1.50 μ; 95% CI: [−28.02, 31.02]; and $p = 0.918$). There were also no CMT differences between right and left eyes ($Z = -0.063$ and $p = 0.963$) nor between sessions ($Z = -0.238$ and $p = 0.815$).

Table 1. Descriptive statistics for all outcome measures.

	N	Mean	St Dev	Median	Min	Max
Age (years)	9	30.0	8.05	28.0	23.0	50.0
Height (in)	9	69.0	2.55	68.0	66.0	73.0
Weight (lbs)	9	180.2	67.5	160.0	130.0	350.0
BGL (mg/dL)	18	94.4	12.8	91.5	79.0	120.0
SBP (mmHg)	18	125.9	17.1	121.5	102.0	170.0
DBP (mmHg)	18	76.8	9.10	78.5	56.0	95.0
IOP–R (mmHg)	18	15.3	4.2	15.0	7.0	22.0
IOP–L (mmHg)	18	15.0	4.4	15.5	7.0	24.0
CCT–R (μ)	18	544.8	42.8	536.0	475.0	613.0
CCT–L (μ)	18	549.4	44.3	543.5	475.0	618.0
CMT–R (μ)	18	266.4	27.6	259.0	232.0	321.0
CMT–L (μ)	18	267.1	30.5	260.0	228.0	315.0
T (pg/mL)	18	248.0	93.8	251.1	107.9	407.1
EST (pg/mL)	18	1.94	0.72	1.85	0.90	3.24
PGT (pg/mL)	18	74.7	41.2	65.1	25.5	203.7

Note. BGL = blood glucose level, SBP = systolic blood pressure, DBP = diastolic blood pressure, IOP = intraocular pressure, CCT = central corneal thickness, CMT = central macular thickness, R = right eye, L = left eye, T = testosterone, EST = estrogen, PGT = progesterone.

3.2. Linear Regression Results

3.2.1. Intraocular Pressure

The complete results of the IOP regression model with robust standard errors are shown in Table 2.

There was a strong relationship between IOP and predictors ($F[11,24] = 12.77$; $p < 0.001$; and adjusted $R^2 = 0.787$), and the model residuals demonstrated homoskedasticity on Breusch–Pagan testing ($\chi^2[1] = 0.104$ and $p = 0.748$). The most significant parameters in the IOP model were height, weight, and SBP (all $p < 0.001$). Indeed, variance in weight and SBP each explained 70% of the variance in IOP measures (i.e., partial $\eta^2 = 0.70$). Variance in height explained over 40% of the variance in IOP. Other significant predictors were BGL ($p = 0.029$ and partial $\eta^2 = 0.183$); CMT ($p = 0.002$ and partial $\eta^2 = 0.344$); T ($p = 0.044$ and partial $\eta^2 = 0.159$); and EST ($p = 0.001$ and partial $\eta^2 = 0.378$).

Table 2. Intraocular pressure regression results using robust standard errors.

Parameter	B	Robust S.E. [a]	t	*p*-Value	95% CI		Partial η^2
					LL	UL	
Intercept	−200.0 ***	43.18	−4.632	0.000	−289.1	−110.9	0.472
Age (years)	−0.106	0.160	−0.663	0.513	−0.437	0.224	0.018
Height (in)	3.137 ***	0.759	4.132	0.000	1.570	4.704	0.416
Weight (lbs)	−0.199 ***	0.027	−7.411	0.000	−0.254	−0.143	0.696
BGL (mg/dL)	0.174 *	0.075	2.315	0.029	0.019	0.329	0.183
SBP (mmHg)	0.634 ***	0.085	7.480	0.000	0.459	0.810	0.700
DBP (mmHg)	−0.070	0.086	−0.817	0.422	−0.246	0.107	0.027
CCT (µ)	−0.013	0.016	−0.834	0.413	−0.045	0.019	0.028
CMT (µ)	−0.160 **	0.045	−3.545	0.002	−0.253	−0.067	0.344
T (pg/mL)	0.011 *	0.005	2.129	0.044	0.000	0.022	0.159
EST (pg/mL)	−4.035 ***	1.056	−3.822	0.001	−6.215	−1.856	0.378
PGT (pg/mL)	0.020	0.017	1.175	0.251	−0.015	0.055	0.054

Note. [a] HC3 Method, * significant at the 0.05 level, ** significant at the 0.01 level, *** significant at the 0.005 level, B = parameter estimate, S.E. = standard error, BGL = blood glucose level, DBP = diastolic blood pressure, SBP = systolic blood pressure, CCT = central corneal thickness, CMT = central macular thickness, T = testosterone, EST = estrogen, PGT = progesterone.

3.2.2. Central Corneal Thickness

There was a moderate relationship between CCT and predictors (F[11,24] = 5.654; $p < 0.001$; and adjusted $R^2 = 0.594$). Model residuals demonstrated homoskedasticity on Breusch-Pagan testing (χ^2[1] = 2.580 and $p = 0.108$). The complete results of the central corneal thickness regression model with robust standard errors are shown in Table 3.

Table 3. Central corneal thickness regression results using robust standard errors.

Parameter	B	Robust S.E. [a]	t	*p*-Value	95% CI		Partial η^2
					LL	UL	
Intercept	−69.00	770.3	−0.090	0.929	−1658.8	1520.8	0.000
Age (years)	−3.424 †	1.704	−2.009	0.056	−6.941	0.093	0.144
Height (in)	15.05	12.05	1.249	0.224	−9.821	39.92	0.061
Weight (lbs)	−1.042	0.623	−1.673	0.107	−2.328	0.244	0.104
BGL (mg/dL)	0.838	1.049	0.799	0.432	−1.326	3.003	0.026
SBP (mmHg)	4.134 *	1.904	2.171	0.040	0.204	8.064	0.164
DBP (mmHg)	−1.362	1.825	−0.746	0.463	−5.129	2.405	0.023
IOP (mmHg)	−2.562	2.958	−0.866	0.395	−8.668	3.543	0.030
CMT (µ)	−1.879 ***	0.491	−3.827	0.001	−2.892	−0.866	0.379
T (pg/mL)	−0.103	0.105	−0.983	0.336	−0.319	0.113	0.039
EST (pg/mL)	−35.22 *	15.14	−2.327	0.029	−66.46	−3.977	0.184
PGT (pg/mL)	0.092	0.224	0.412	0.684	−0.371	0.555	0.007

Note. [a] HC3 Method, † significant at the 0.10 level, * significant at the 0.05 level, *** significant at the 0.005 level, B = parameter estimate, S.E. = standard error, BGL = blood glucose level, DBP = diastolic blood pressure, SBP = systolic blood pressure, IOP = intraocular pressure, CMT = central macular thickness, T = testosterone, EST = estrogen, PGT = progesterone.

Significant parameters in the CCT model were CMT ($p = 0.001$), EST ($p = 0.029$), and SBP ($p = 0.040$). Approximately 38% of the variance in CCT was explained by CMT, while less than half of that (18.4% and 16.4%) was explained by the variance in EST and SBP, respectively. In addition, 14.4% of the variance in CCT could be explained by the variance in age, but the parameter estimate did not reach $p = 0.05$ statistical significance.

3.2.3. Central Macular Thickness

There was a very strong relationship between CMT and predictors (F[11,24] = 44.74; $p < 0.001$; and adjusted $R^2 = 0.954$). Plots of standard residuals vs. modeled CMT appeared homoscedastic, but they demonstrated heteroskedasticity on Breusch–Pagan testing

($\chi^2[1] = 4.600$ and $p = 0.032$). The results of the central macular thickness regression models with robust standard errors are shown in Table 4.

Table 4. Central macular thickness regression results using robust standard errors.

Parameter	B	Robust S.E. [a]	t	*p*-Value	95% CI		Partial η^2
					LL	UL	
Intercept	−747.0 ***	148.5	−5.029	0.000	−1053.5	−440.4	0.513
Age (years)	−1.854 ***	0.463	−4.004	0.001	−2.810	−0.899	0.401
Height (in)	14.73 ***	1.970	7.476	0.000	10.66	18.79	0.700
Weight (lbs)	−0.704 ***	0.131	−5.371	0.000	−0.975	−0.433	0.546
BGL (mg/dL)	1.088 ***	0.241	4.515	0.000	0.591	1.585	0.459
SBP (mmHg)	2.127 ***	0.537	3.963	0.001	1.019	3.234	0.396
DBP (mmHg)	−0.578	0.417	−1.386	0.179	−1.439	0.283	0.074
IOP (mmHg)	−2.335 **	0.805	−2.903	0.008	−3.996	−0.675	0.260
CCT (μ)	−0.140 *	0.056	−2.495	0.020	−0.256	−0.024	0.206
T (pg/mL)	−0.020	0.032	−0.630	0.535	−0.087	0.046	0.016
EST (pg/mL)	−17.73 ***	3.162	−5.608	0.000	−24.26	−11.21	0.567
PGT (pg/mL)	0.072	0.056	1.300	0.206	−0.042	0.187	0.066

Note. [a] HC3 Method, * significant at the 0.05 level, ** significant at the 0.01 level, *** significant at the 0.005 level, B = parameter estimate, S.E. = standard error, BGL = blood glucose level, DBP = diastolic blood pressure, SBP = systolic blood pressure, IOP = intraocular pressure, CMT = central macular thickness, T = testosterone, EST = estrogen, PGT = progesterone.

The most significant parameters in the CMT model were height, weight, EST, and BGL (all $p < 0.001$). Height was the most influential parameter, explaining 70% of the variance in CMT, while EST, weight, and BGL accounted for 54.6%, 56.7%, and 45.9% of the variance in CMT, respectively. Age and SBP were also significant predictors ($p = 0.001$), each accounting for approximately 40% of the variance in CMT. Other significant predictors of CMT were IOP ($p = 0.008$ and partial $\eta^2 = 0.260$) and CCT ($p = 0.020$ and partial $\eta^2 = 0.206$).

3.3. Bivariate Correlations

Bivariate correlation analyses were also used to examine all relationships between physical characteristics, metabolic markers, ocular parameters, and hormone levels. Spearman ranked correlations, rho (ρ), are reported in Table 5.

Table 5. Bivariate correlations of all measures.

	Age	Ht	Wt	BGL	SBP	DBP	IOP	CCT	CMT	T	EST	PGT
Age	1.00	0.72 ***	0.87 ***	−0.04	0.08	−0.13	0.12	−0.27	0.09	−0.44 †	−0.13	−0.27
Ht	--	1.00	0.92 ***	0.23	0.27	0.13	0.05	0.56 *	0.45 †	−0.38	0.04	−0.05
Wt	--	--	1.00	0.18	0.37	0.16	0.07	−0.36	0.37	−0.49 *	−0.04	−0.14
BGL	--	--	--	1.00	0.47 *	0.81 ***	0.09	−0.39	0.78 ***	−0.41 †	0.17	0.06
SBP	--	--	--	--	1.00	0.75 ***	0.49 *	0.13	0.71 ***	−0.57 *	−0.06	−0.26
DBP	--	--	--	--	--	1.00	0.24	−0.10	0.78 ***	−0.50 *	−0.05	−0.18
IOP	0.04	−0.22	−0.07	−0.09	0.34	0.09	0.86 ***	0.29	0.15	−0.12	−0.27	−0.30
CCT	−0.23	−0.60 **	−0.35	−0.35	0.12	−0.07	0.37	0.97 ***	−0.32	0.13	−0.31	−0.25
CMT	0.13	0.50 *	0.45 †	0.78 ***	0.74 ***	0.79 ***	−0.18	−0.30	0.98 ***	−0.58 *	0.05	−0.21
T	--	--	--	--	--	--	0.17	0.09	−0.57 *	1.00	0.21	0.61 **
EST	--	--	--	--	--	--	−0.20	−0.36	0.08	--	1.00	0.78 **
PGT	--	--	--	--	--	--	−0.14	−0.29	−0.15	--	--	1.00

Note. Spearman ranked correlations (ρ) reported (N = 18; 9 subjects × 2 sessions). IOP, CCT, and CMT correlations are presented in the upper right for the right and lower left for the left eye. The shaded cells represent the correlations between right and left eyes. -- indicates the same correlation for the right and left eyes, † significant at the 0.10 level, * significant at the 0.05 level, ** significant at the 0.010 level, *** significant at the 0.005 level, Ht = height, Wt = weight, BGL = blood glucose level, DBP = diastolic blood pressure, SBP = systolic blood pressure, IOP = intraocular pressure, CMT = central macular thickness, T = testosterone, EST = estrogen, PGT = progesterone.

The positive relationships of age to both height ($\rho = 0.72$) and weight ($\rho = 0.87$) were significant. There was also a trend toward a negative relationship between age and T levels

($\rho = -0.44$). Not surprisingly, there was a strong positive relationship of weight with height ($\rho = 0.92$) but a weaker negative relationship between weight and T levels ($\rho = -0.49$). BGL was positively associated with both SBP ($\rho = 0.49$) and DBP ($\rho = 0.81$) but trended toward a negative relationship with T levels ($\rho = -0.41$). T levels were also negatively associated with SBP ($\rho = -0.57$) and DBP ($\rho = -0.50$). PGT levels were positively associated with both T ($\rho = 0.61$) and EST ($\rho = 0.78$) levels.

There were also several bivariate relationships involving ocular parameters, which are shown separately in Table 5 for right and left eyes. IOP was positively associated with SBP, significantly for the right eye ($\rho = 0.49$) but not the left eye. There were significant negative relationships between height and CCT for both the right ($\rho = 0.56$) and left ($\rho = 0.60$) eyes. There were strong positive bivariate associations between BGL, SBP, DBP, and CMT in each ($\rho > 0.70$ for all comparisons). CMT in both eyes was positively related to height and weight but negatively correlated with T levels ($\rho \sim -0.60$ in each eye).

3.4. Post Hoc Power Analysis

We performed post hoc power analyses using G*Power (Version 3.1.9.7) for both the regression and correlation models. For the fixed IOP, CCT, and CMT linear multiple regression models, we used a number of observations (= 36) (9 subjects × 2 eyes × 2 sessions), and $\alpha_{crit} = 0.05$, which yielded $F_{crit}[11,24] = 2.216$, exceeding in all models ($F_{IOP} = 12.769$, $F_{CCT} = 5.654$, and $F_{CMT} = 44.740$). Using the adjusted R^2 from each model yielded effect sizes (f^2) of 3.695, 1.463, and 13.71 and post hoc powers ($1-\beta$) of 1.000, 0.994, and 1.000 for IOP, CCT, and CMT, respectively.

The G*Power bivariate correlation normal model with a sample size of 18 (9 subjects × 2 sessions) and a two-tailed $\alpha_{crit} = 0.05$ yielded $r_{crit} = 0.468$. Many of our correlations exceeded that level. However, with a sample size of 18 (9 subjects × 2 sessions each), an r_{crit} of 0.605 is required to achieve a power of 0.80. Only the associations between CMT and metabolic parameters, such as BGL ($\rho = 0.78$), SBP ($\rho = 0.71$), and DBP ($\rho = 0.78$), exceeded that critical level. The significant relationship between CMT and T levels ($\rho = 0.58$ for the right eye) was, however, slightly underpowered ($1-\beta = 0.753$). Conversely, as many of our significant findings were approximately $|\rho| = 0.50$, an a priori analysis suggests that a sample size of 23 would be required to achieve a power of 0.80.

4. Discussion

This study investigated the relationships between various physical, physiological, and hormonal parameters and intraocular pressure (IOP), central corneal thickness (CCT), and central macular thickness (CMT) in a sample of nine men. The results provide insights into the factors influencing these ocular measurements, with significant findings in the areas of systemic and ocular parameters.

4.1. Primary Outcomes

The regression model for IOP indicated that height, weight, blood glucose level (BGL), systolic blood pressure (SBP), central macular thickness (CMT), testosterone (T), and estradiol (EST) were significant predictors. Notably, weight and SBP were the most influential factors, each explaining 70% of the variance in IOP. These findings suggest that systemic factors, such as weight and blood pressure, have a substantial impact on IOP.

The strong effect of weight on intraocular pressure in the regression model is not surprising, as several studies have demonstrated this association. Increases in body weight are linked to higher IOP, even after adjusting for age, hypertension, and diabetes mellitus [24,25], and bariatric surgery has been shown to reduce IOP [26]. Khan et al. [24] further found the overall pooled relative risk (RR) for the relationship between body mass index

(BMI) and elevated IOP to be 1.06 (95 CI%, [1.04, 1.07]), indicating that for each unit increase in BMI, the likelihood of having higher-than-normal IOP increases by 6%. Additionally, two studies examining the effects of bariatric surgery found significant postoperative decreases in IOP, further supporting the link between body weight and IOP regulation. While these studies have reported an increase in IOP associated with a higher BMI in individuals classified as overweight or obese, our data indicate that this correlation may extend even to variations in height and weight within the normal range.

The positive associations between systolic blood pressure (SBP) and IOP are consistent with previous research showing that elevated blood pressure can increase IOP, as demonstrated in the Framingham Eye study II, Beaver Dam study, and Barbados study in a Black population [27,28]. Research in a Japanese population has shown that elevated blood pressure was associated with increased IOP or ocular hypertension, which was greater for SBP than DBP elevations [29]. Conversely, this association was not found in a study on a Nepalese population [30]. However, the correlation between SBP and IOP is not always as clear in individuals with normal blood pressure. The effects of blood pressure on intraocular pressure might be linked to aqueous humor dynamics, including both its production and drainage. Elevated blood pressure increases the ultrafiltration-dependent production of aqueous humor when blood pressure is pathologically elevated, which can temporarily elevate IOP until the excess aqueous humor is drained. However, this mechanism has minimal impact for lower levels of blood pressure. Another factor that has an exponential effect on IOP elevations is venous pressure, which can impair the outflow of the aqueous humor and thereby increase IOP [31]. Whether this mechanism played a role in our population remains unclear, as we did not measure episcleral venous pressure.

It is interesting to note that the relationship of systolic BP and IOP was significant in the right (ρ = 0.49) but not the left (ρ = 0.34) eye. In a large-scale study, Bhorade et al. [32] reported, for the Ocular Hypertension Study Group, a relatively low inter-eye IOP correlation (ρ~0.70). Our IOP correlation was higher (ρ = 0.86) but still much lower than our CCT (ρ = 0.97) and CMT (ρ = 0.98) inter-eye correlations. Related to the work of Arora et al. [31], Majcher et al. [33] reported inter-eye IOP differences between the dependent (or lower) and non-dependent (higher or more elevated) eye in lateral decubitus (i.e., "side") sleepers. They further found that the effect of postural changes was not immediate, with the non-dependent eye's IOP taking 30–60 min to stabilize. While we did not gather data on sleeping patterns or postures, it is likely that we measured IOP within an hour of waking for some subjects. This relationship of blood pressure, intraocular pressure, and postural patterns remains an interesting future line of inquiry.

Height also emerged as a significant factor in our regression analysis, accounting for over 40% of the variance in IOP. While the influence of height on IOP, though significant, is less commonly reported, it may warrant further investigation. Studies performed in a Japanese population observed that taller individuals had a lower prevalence of open angle glaucoma (POAG), while the Beijing Eye Study 2011 found no correlation between body height and IOP levels [34]. In our study, height explained a substantial portion of the variance, suggesting that increased height might be linked to higher body weight, which could contribute partly to the elevations in IOP. However, we did not find a direct correlation between height and IOP, independent of body weight. The separate effects of height or weight on IOP remain to be determined in larger subsequent studies.

Variability in sex hormones also contributed to IOP variance in our study population. Estrogens accounted for 38% of the observed IOP variance, while testosterone accounted for 16%. The influence of testosterone in IOP regulation has been evaluated in women with polycystic ovarian syndrome (PCOS), a condition marked by hyperandrogenism and obesity. Studies on PCOS link testosterone and estrogen levels, as well as BMI, to IOP [35];

however, hyperandrogenism remains the primary factor influencing elevated IOP. Among men, those with plasma testosterone levels above 3.0 ng/mL tend to exhibit higher levels of IOP, while levels below 3.0 ng/mL are not associated with this elevation [16]. In our study, we did not categorize participants by specific salivary testosterone levels, as their levels were considered within normal limits [36], yet we still found a significant positive association between salivary testosterone values and IOP. Furthermore, additional studies have linked variability in testosterone metabolism to primary open-angle glaucoma in men but not in women [37], which exposes the complexity of the impact of testosterone on IOP regulation.

The impact of estrogen in ocular parameters is typically investigated in women. Although plasma estradiol levels or HRT in postmenopausal women have not shown a clear association with POAG risk [38,39], estrogen-alone therapy in postmenopausal women has been associated with a slight IOP reduction of 0.5 mm Hg [40]. Furthermore, estrogen polymorphism has been correlated with IOP, POAG, or ocular hypertension in women but not in men [18]. Currently, there is limited evidence to support a direct impact of estrogen levels on IOP in men. Our study, however, suggests such regulation in IOP by estrogens in young healthy men, contributing to a broader understanding of hormonal influence on ocular health.

The CCT regression model revealed that central macular thickness (CMT), estrogen (EST), and SBP were significant predictors. CMT was the most influential, explaining 38% of the variance in CCT. This relationship between CMT and CCT suggests a structural link between different parts of the eye, where changes in macular thickness may influence corneal thickness. However, this correlation is not well-established in the literature. Contrarily to our data, Zhou et al. found no correlation between both parameters [41].

Estrogens and SBP contributed 18.4% and 16.4% of the variance in CCT, respectively. Earlier studies have shown a linear correlation between CCT and serum estrogen levels, with a significant decline in CCT in postmenopausal women compared to premenopausal women [42]. There is also evidence of CCT fluctuations during the menstrual cycle, with the highest values observed at the end of the cycle and the lowest at the start, coinciding with an abrupt change in hormone levels [43]. Oral contraceptive use has also been associated with increased CCT [44]. Most studies on the correlation of estrogens with CCT have been performed in women, and there is a scarcity of data for men. Van et al. did observe that corneal curvature was correlated with the levels of estrogens in patients with keratoconus [45], including both men and women. However, in animal models, Walter et al. found no significant effect of estrogens on CCT [46]. Overall, the evidence that estrogen levels affect corneal thickness remains inconclusive. The present significant role of estrogens in male CCT variation highlights the potential impact of hormonal levels on ocular structures, which could be crucial for understanding sex-related differences in eye physiology and disease prevalence.

Age also appeared to negatively influence CCT, explaining 14.4% of the variance, although it did not reach statistical significance. Most studies suggest similar significant inverse correlations between age and CCT, with a decrease of approximately 2–10 µm per decade [47–49], although some studies did not find this association when the population was relatively young [50].

For CMT, the regression model identified height, weight, estrogens, and BGL as highly significant predictors. Height was the most influential, explaining 70% of the variance, followed by estrogens (54.6%), weight (56.7%), and blood glucose (45.9%). Previous research has shown a positive correlation between height and CMT, foveal thickness, and macular thickness in a Japanese population [51]. Weight was also a major factor, explaining 56.7% of the variance. Studies have shown that CMT is higher in individuals with pre-obesity,

thinning out in the obese group [52], but most research has focused on BMI rather than body height or body weight specifically. For instance, studies have found thinner central foveal thickness in individuals with obesity-related hypertension [53], but no such association was observed in a study limited to women [54]. The significant impact of height and weight on CMT suggests that overall body size and composition may affect retinal thickness, potentially through mechanisms related to blood flow and metabolic activity.

Although estrogens explained 54.6% of the variance in our study, recent reports have not found a difference in CMT between postmenopausal and premenopausal women [55]. We know of no studies reporting estrogen effects on CMT in premenopausal women or in men. While we also found no bivariate relationships between estrogen and CMT in our study, the influence of estrogens on the CMT regression model in our study supports the notion that hormonal levels play a critical role in retinal health, but further research is needed to clarify this effect.

Blood glucose levels explained 45.9% of the variance in CMT in our non-diabetic population; however, most studies in the literature focus on diabetic or prediabetic patients. CMT has been associated with macular edema and HbA1C control in diabetic patients [56] but not in non-diabetic patients. There is also evidence that dysglycemia is linked to macular thinning, particularly in the nasal region [57]. Our findings in normo-glycemic subjects suggest that assessing glycemia during routine ocular evaluations could be valuable, as it may influence CMT readings.

Age and SBP also significantly influenced CMT in our study, each accounting for approximately 40% of the variance. This result is similar to the findings in a previous study on older adults [58]. Pediatric studies have also shown a positive correlation between central macular thickness and central macular volume with age [59,60]. However, this relationship has not been consistently found in adults [61]. In fact, some studies report an inverse correlation between age and retinal nerve fiber layer (RNFL) or GC-IPL (ganglion cell–inner plexiform layer) thickness [62–64], while others show a positive association [65–67]. Together with our findings, these results underscore the complex interplay between systemic health factors and retinal structure.

Finally, bivariate correlations revealed significant relationships between several variables. For instance, there were strong positive correlations between height and weight (ρ = 0.92) as well as systolic and diastolic blood pressure (ρ = 0.75). These findings, well-established in the literature [68,69], both validate our predictors and provide additional context for understanding the present regression results. Further, while EST levels were significant predictors in IOP, CCT, and CMT regression models, T levels were only significant in the IOP regression model. However, the only significant bivariate relationship between hormone levels and ocular parameters was the negative correlation between macular thickness and T levels ($r \sim -0.6$ in both eyes). T levels were also negatively correlated with age, weight, BGL, SBP, and DBP, a result seen nearly uniformly in the literature (e.g., [70,71]). These results highlight, in men, the interconnected nature of systemic health parameters and a potential therapeutic role for testosterone in ophthalmology and optometry.

4.2. Limitations

Our primary investigations (i.e., linear regression models using robust standard errors) appeared to be adequately powered for the IOP and CMT—but not the CCT—models. Overall, the correlation models were less powered. Post hoc power analyses from pilot studies are mostly used to validate the results for the specific small sample used and should be used very conservatively when informing future studies [72]. However, an a priori G*Power analysis for bivariate correlations suggests a minimum sample of 23 to achieve a power of 0.80 with the $|r| = 0.50$ we found for many bivariate relationships. While

investigating these bivariate relationships was not the primary goal of our analysis, this study's small sample size remains a notable limitation, potentially affecting other inferences. Further, the analysis of the CMT model did indicate unequal variation across predictors (i.e., heteroskedasticity), which could indicate low generalizability to other sub-groups of men. This could be exacerbated by our use of robust standard errors, which allows for outliers to be included in predictors (e.g., age and progesterone both included outliers). In future analyses with more subjects, linear regression models could be weighted based on observed variance, but our limited number of subjects precluded unbiased weighting. Our data collection window was only one semester (about four months), and most of our participants came from our student populations. Further, we offered no academic inducements (e.g., no extra credit, etc.), and the testing was relatively invasive to privacy and took place early in the morning before classes began. Males also only make up approximately 30% of students in optometry programs [73], and our population is no different [74]. While the racial and ethnic makeup of our participants (two white/non-Hispanics, two white/Hispanics, and two Asians) mirrors our local community, the sample size was too small for an analysis of these important variables. Overall, limiting the sample to young, healthy men may have limited our pool as well as the applicability of the results to broader populations with common systemic conditions, such as diabetes and hypertension.

Additionally, there are limitations from our use of both eyes in the analysis. From the body of evidence concerning the treatment of separate eyes in ophthalmic studies, some authors suggest using general estimable equations with eye as repeated measures when data have been collected from both eyes (e.g., [75,76]). Ideally, with our sample, we would then set up four repeated measures for each of the nine subjects (e.g., IOP—right eye, 1st session; IOP—right eye, 2nd session; IOP—left eye, 1st session; IOP—left eye, 2nd session) with all other parameters (age, height, weight, BGL, SBP, DBP, CCT, CMT, T, EST, and PGT) serving as covariates. (This would be repeated for CCT and CMT.) We could not do this, because IOP, CCT, and CMT effects are different between the eyes (e.g., right-eye CCT and CMT effects on the IOP in the right eye are different than left-eye CCT and CMT effects on the IOP in the left eye), and these differences are particularly important to our analysis. Further, it is impossible to nest CCT and CMT data from right and left eyes into that type of repeated-measures design. The best we could do is average the values from two eyes for each ocular parameter being used as a predictor. This, however, would yield two observation equations that are identical between the right and left eyes for each session. To avoid this, we could have also used separate analyses for the right and left eyes, treating session as the only repeated measure. There are problems with this approach as well. First, it doubles the size of the results section, as we would need to report parameter estimates for both the right and left eyes. We believe this is not as clean as presenting the results from a single-nested approach. Second, and perhaps more importantly, many of our parameters were not normally distributed. Linear regressions with robust standard errors are the best estimates of multivariate ranked correlations and are typically performed using a univariate analysis of variance with the repeated measures included as separate (in our case, 36) observations. Regarding the sample size, there is evidence that inter-correlated data from right and left eyes inflate the calculated post hoc power, and it has been suggested that the sample size be adjusted based on inter-eye correlations [77]. In our case, with 0.87, 0.97, and 0.96 inter-eye correlations for IOP, CCT, and CMT (see Table 5), we would adjust the N by 44% for IOP (N = 20) and 49% for CCT and CMT (N = 19). Our post hoc power ($1-\beta$) would then be 0.965 (IOP model), 0.530 (CCT model), and 1.00 (CMT model). Therefore, with this conservative post hoc approach, our IOP and CMT models are validated, but the CCT model is underpowered. We then suggest that future studies

weigh the benefits of collecting monocular data against the statistical challenges of using data from both eyes.

The present study's cross-sectional design also precludes conclusions about causality. Further, there were many significant bivariate correlations between the predictors. Under these conditions of multicollinearity, the set of normal equations that is inverted to calculate the final estimated parameters can become singular (i.e., cannot be mathematically inverted). It may have then been advisable to eliminate correlated predictors from the regression models. For example, SBP and DBP were significantly positively correlated, and models combining SBP and DBP would have been eliminated. Since additional predictors will almost always increase the overall effect size of models, it is important to have the same number of predictors when comparing model effect sizes (i.e., R^2 for IOP, CCT, and CMT). Lastly, height and weight were strongly positively correlated, but—as with SBP and DBP—it was of interest to observe the separate effects of both height and weight on IOP, CCT, and CMT models. Therefore, we chose to simply retain all directly measured predictors in all three primary models.

5. Conclusions

This pilot study identifies several significant predictors of IOP, CCT, and CMT, highlighting the roles of systemic health parameters and hormonal levels in ocular physiology. The findings suggest that weight; blood pressure; and hormonal levels, such as estradiol, have substantial impacts on these ocular measurements. Testosterone's strong association with certain systemic health markers, such as systolic blood pressure, is commonly found in the literature, but ours appears to be the first study demonstrating estrogen's effects on ocular biometrics in men. To avoid overinterpretation of our findings, it is important to concede that certain aspects of this study remain underpowered, even with a nested univariate approach treating the right and left eyes as separate observations. Future research with larger, longitudinal designs with more diverse populations is then needed to confirm these relationships and elucidate underlying mechanisms.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are openly available on FigShare [78].

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Conflicts of Interest: The authors have reported portions of these data in continuing education lectures and in abstract form as meeting scientific reports but declare no further potential conflicts of interest in authorship or reporting.

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