Multifactorial Analysis of Intraocular Pressure, Corneal and Macular Thickness: The Role of Hormonal, Metabolic, and Physical Characteristics in Men

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Article

Multifactorial Analysis of Intraocular Pressure, Corneal and Macular Thickness: The Role of Hormonal, Metabolic, and Physical Characteristics in Men

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Abstract: (1) **Background/Objectives:** This study aims to address the research gap on the interplay between ocular and systemic parameters as well as hormones—particularly estrogen and progesterone—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. Ours appears to be the first study demonstrating estrogen's effects on ocular structure or physiology in men, but 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

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, 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 the IOP readings, particularly when non-contact tonometry is used [7]. Additionally, 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

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between ocular and systemic parameters. Additionally, while there have been numerous 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 in males. This study aims to address these gaps by evaluating the impact of extrinsic as well as intrinsic factors on ocular parameters and their regulation, with the goal of improving our understanding and assessment of ocular health.

2. Materials and Methods

2.1. Participants

Sixteen men volunteered for the study. Exclusion criteria included a clinical history of diabetes mellitus (DM), hypertension (HTN), thyroid disease, current oral or topical ophthalmic anti-inflammatory medication use, history of glaucoma, and refractive surgery. We excluded one volunteer for a history of diabetes. 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 15 subjects. Due to facility and scheduling constraints, metabolic data (e.g., blood glucose level [BGL] and blood pressure) measurements were missing for six participants. Ocular data (IOP, CCT, and/or CMT) were missing for two subjects, and hormone data were missing for one subject. Overall, our analyses were then based on complete data from nine participants.

2.2. Scheduling and Procedure

Participants were scheduled for two sessions two weeks apart. To minimize the confounding diurnal effects on intraocular pressure [18–20], 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) measurement was assessed using the Icare® ic100 rebound tonometer, 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 from Accutome, Inc., Malvern, PA. 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 CirrusTM 4000 (Zeiss spectral domain optical coherence tomography) with a 512 x 128 macular scan pattern. Reliable scans (signal strength ≥ 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 (SCA), (Salimetrics, Inc, State College, PA) into a cryo-vial and stored at -20°C until assayed for estrogen (EST), progesterone (PGT), and testosterone (T) using commercially available enzyme immunoassay (EIA) kits (Salimetrics, Inc, State College, PA). 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 hour 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 [21].

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2.5. Data Analysis

We first compared all variables to normal distributions using the Kolmogorov-Smirnov goodness of fit test. All measures were normally distributed other than age, weight, IOP, and PGT. IOP inter-eye and between session differences were compared via non-parametric Mann-Whitney tests. CCT and CMT 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 x 2 sessions x 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.

3. Results

3.1. Descriptive Results

Descriptive results for all outcome measures for all subjects are shown in Table 1.

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 (m)	18	544.8	42.8	536.0	475.0	613.0
CCT – L (m)	18	549.4	44.3	543.5	475.0	618.0
CMT – R (m)	18	266.4	27.6	259.0	232.0	321.0
CMT – L (m)	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.

IOP was essentially equivalent on paired comparisons between the right and left eyes (Z = -0.175, p = 0.864) and between sessions (Z = 0.243, p = 0.808). There were no CCT differences between right and left eyes (*Mean difference [MD]* = -1.83 μ, 95% *CI*: [-21.56, 17.91], p = 0.853) nor between sessions (*MD* = -3.44 μ, 95% *CI*: [-23.18, 16.29], p = 0.728). There were also no CMT differences between right

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and left eyes (*MD* = -0.272 μ, 95% *CI*: [-14.16, 13.62], $p = 0.969$) nor between sessions (*MD* = 1.30 μ, 95% *CI*: [-12.60, 15.19], $p = 0.852$).

3.2. Linear Regression Results

3.2.1. Intraocular Pressure

There was a strong relationship between IOP and predictors (F [11,24] = 12.77, $p < 0.001$, adjusted $R^2 = 0.787$), and the model residuals demonstrated homoskedasticity on Breusch-Pagan testing (χ^2[1] = 0.104, $p = 0.748$). The complete results of the IOP regression model with robust standard errors are shown in Table 2.

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

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

Note. [a]HC3 Method, 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.

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 ($p = 0.029$, partial $\eta^2 = 0.183$), CMT ($p = 0.002$, partial $\eta^2 = 0.344$), T ($p = 0.044$, partial $\eta^2 = 0.159$), and EST ($p = 0.001$, partial $\eta^2 = 0.378$).

3.2.2. Central Corneal Thickness

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

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 statistical significance ($p = 0.056$).

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

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

Note. [a]HC3 Method, 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.

3.2.3. Central Macular Thickness

There was a very strong relationship between CMT and predictors (F [11,24] = 44.74, $p < 0.001$, adjusted $R^2 = 0.954$). Plots of standard residuals vs. modeled CMT appeared homoscedastic, but they demonstrated heteroskedasticity on Breusch-Pagan testing ($\chi^2[1] = 4.600$, $p = 0.032$). 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 h^2
					LL	UL	
Intercept	-747.0	148.5	-5.029	0.000	-1053.5	-440.4	0.513
Age	-1.854	0.463	-4.004	0.001	-2.810	-0.899	0.401
Height	14.73	1.970	7.476	0.000	10.66	18.79	0.700
Weight	-0.704	0.131	-5.371	0.000	-0.975	-0.433	0.546
BGL	1.088	0.241	4.515	0.000	0.591	1.585	0.459
SBP	2.127	0.537	3.963	0.001	1.019	3.234	0.396
DBP	-0.578	0.417	-1.386	0.179	-1.439	0.283	0.074
IOP	-2.335	0.805	-2.903	0.008	-3.996	-0.675	0.260
CCT	-0.140	0.056	-2.495	0.020	-0.256	-0.024	0.206
T	-0.020	0.032	-0.630	0.535	-0.087	0.046	0.016
EST	-17.73	3.162	-5.608	0.000	-24.26	-11.21	0.567
PGT	0.072	0.056	1.300	0.206	-0.042	0.187	0.066

Note. [a]HC3 Method, 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

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the variance in CMT. Other significant predictors of CMT were IOP ($p = 0.008$, partial $\eta^2 = 0.260$) and CCT ($p = 0.020$, partial $\eta^2 = 0.206$).

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 correlation of weight and intraocular pressure 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 [22,23], and bariatric surgery has been shown to reduce IOP [24]. Khan et al. [22] 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 higher BMI in individuals classified as overweight or obese, our data indicates that this correlation may extend even to variations in height and weight within the normal range.

The positive correlation between systolic blood pressure (SBP) and IOP is 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 black population [25,26]. Research in a Japanese population have shown that elevated blood pressure was associated with increased IOP or ocular hypertension, which was greater for SBP than DBP elevations [27]. Conversely, this association was not found in a study of the Nepalese population [28]. 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 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 outflow of the aqueous humor and thereby increasing IOP [29]. Whether this mechanism played a role in our population remains unclear, as we did not measure episcleral venous pressure.

Height also emerged as a significant factor in our study, 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 [30]. 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, whether there is a direct correlation between height and IOP, independent of body weight, remains to be determined.

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

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(PCOS), a condition marked by hyperandrogenism and obesity. Studies on PCOS link testosterone and estrogens levels, as well as BMI, to IOP [31]; 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 categorized participants by specific salivary testosterone levels, as their levels were considered within normal limits [32], 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 [33], 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 [34,35], estrogen-alone therapy in postmenopausal women has been associated with a slight IOP reduction of 0.5 mm Hg [36]. Furthermore, estrogens polymorphism has been correlated with IOP, POAG or ocular hypertension in women but not in men [37]. Currently, there is limited evidence to support a direct impact of estrogens 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 [38].

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 [39]. 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 abrupt change in hormone levels [40]. Oral contraceptive use has also been associated with increased CCT [41]. 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 [42] including both men and women. However, in animal models, Walter et al. found no significant effect of estrogens on CCT [43]. 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 influence CCT, explaining 14.4% of the variance, although it did not reach statistical significance. Most studies suggest a significant inverse correlation between age and CCT, with a decrease of approximately 2–10 μm per decade [44–46] although some studies did not find this association when the population was relatively young [47].

For CMT, the 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 [48]. 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 [49] 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 [50] but no such association was observed in a study limited to women [51]. 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.

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Although estrogens explained 54.6% of the variance in our study, recent reports have not found difference in CMT between postmenopausal and premenopausal women [52]. We know of no studies reporting estrogen effects on CMT in pre-menopausal women or in men. The influence of estrogens on CMT 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 [53], but not in non-diabetic patients. There is also evidence that dysglycemia is linked to macular thinning, particularly in the nasal region [54]. 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 findings in a previous study of older adults [55]. Pediatric studies have also shown a positive correlation between central macular thickness and central macular volume with age [56,57]. However, this relationship has not been consistently found in adults [58]. 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 [59–61] while others show a positive association [62–64]. Together with our findings, these results underscore the complex interplay between systemic health factors and retinal structure.

4.2. Limitations

The study's small sample size ($N = 9$) is a notable limitation, potentially affecting inferences. For example, 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, as our limited number of subjects precluded unbiased weighting. However, our data collection window was about six months, and most of our participants came from our student population. Males only make up approximately 30% of students in optometry programs [https://optometriceducation.org/wp-content/uploads/2024/05/Enrollment-Gender.pdf], and our population is no different [https://optometriceducation.org/wp-content/uploads/2022/03/ASCO-Student-Data-Report-2020-21-updated-3-29-22.pdf]. Additionally, the exclusion of individuals with certain systemic conditions (e.g., diabetes, hypertension) may have limited our pool as well as the applicability of the results to broader populations with these conditions.

The present study's cross-sectional design also precludes conclusions about causality. Further, while not reported here, 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. However, CCT and CMT were significantly negatively correlated ($r = -0.380$, $p = 0.046$; bivariate analysis not reported here), and models combining CCT and CMT 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 are almost always going to demonstrate high bivariate correlations, but it was of interest to observe the separate effects of both height and weight on IOP, CCT, CMT models. Therefore, we chose to simply retain all predictors in all three primary models.

5. Conclusions

This 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. Ours appears to be the first study demonstrating estrogen's effects on ocular biometrics in men, but future research with larger, longitudinal designs with more diverse populations is needed to confirm these relationships and elucidate underlying mechanisms.

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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 conflict of interest in authorship or reporting.

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