



Cross Sectional Study among Intraocular Pressure, Mean Arterial Blood Pressure, and Serum Testosterone according to the Anthropometric Obesity Indices in Korean Men

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Purpose: To investigate the association between intraocular pressure (IOP) and serum testosterone according to the severity of obesity.

Materials and Methods: We investigated the correlation of IOP-testosterone according to the anthropometric obesity indices, such as obesity index (OI), body mass index (BMI), and waist circumference to height ratio (WtHR). Each of the obesity indices was classified into three groups: normal, overweight, and obesity. In addition, the association of IOP-testosterone was compared between testosterone 3.0 ng/mL below and above.

Results: Total of 3,949 participants, the mean age was 58.86±10.06 years, mean IOP was 14.40±2.61 mmHg, mean arterial blood pressure (MAP) was 93.67±11.47 mmHg, and mean serum testosterone was 4.21±1.83 ng/mL. The association of MAP and IOP was significantly positively correlated according to the severity of obesity, but testosterone showed a significant negative relationship ($p<0.05$). IOP was significantly correlated with OI and BMI, but MAP and testosterone were correlated with all anthropometric obesity indices ($p<0.05$). The relationship of IOP and testosterone was significantly associated with only normal groups according to the degree of obesity ($p<0.05$). The IOP in patients with testosterone above 3.0 ng/mL was significantly higher than testosterone below 3.0 ng/mL ($p<0.05$).

Conclusions: The correlation of IOP-testosterone has a significantly positive relationship, in case of healthy men with normal weight by OI or BMI.

Keywords: Anthropometry; Intraocular pressure; Obesity; Testosterone

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INTRODUCTION

Glaucoma is a progressive optic neuropathy that

results in a characteristic change in visual acuity, which results in permanent vision loss if not properly treated [1]. As the study of intraocular pressure (IOP)

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is conducted for early diagnosis of glaucoma, obesity is known to induce excess fat in the body and cause high IOP, thus impacting the progression of glaucoma [2,3]. As obesity is known to be a risk factor for glaucoma, the health factors that measure the degree of obesity, obesity index (OI), body mass index (BMI), body shape index (ABSI), and waist to height ratio (WtHR), are epidemiologically studied in relation to IOP [4-10].

Recently, the incidence of obesity is increasing due to changes in eating habits and lack of physical activity. Obesity not only affects blood vessels but also relates to serum testosterone, which is associated with testosterone deficiency [11-14]. Some researchers reported that obesity is the clinical condition most strongly associated with lowering testosterone concentration in men [12,13]. However, it seems to be that the association between obesity and serum testosterone is not simple [11]. Also, the high concentration of serum testosterone increases IOP. And, it is related to reduce the activity of endothelial nitric oxide synthase (eNOS) in the trabecular meshwork, which is 5α -reductase abundant tissue. Testosterone is metabolized to dihydrotestosterone (DHTS) at trabecular meshwork by 5α -reductase. DHTS reduced eNOS activity in the trabecular meshwork and suppressed the outflow facility of aqueous, eventually increasing IOP [15]. In general, IOP is affected by the concentration of serum testosterone or obesity. Therefore, maintaining proper level of blood testosterone along with losing body weight positively affects the control of IOP in order to improve the vascular function of vessels induced by obesity or to suppress the associated inflammatory response due to systemic inflammation, such as diabetes or hypertension.

As for the relationship between IOP and serum testosterone, the higher the testosterone, the higher the IOP in the primary open-angle glaucoma in women with menopause [13,14,16,17]. However, the IOP elevation mechanism by testosterone in men is not completely clarified, nevertheless the testosterone metabolism gene variants related to intracrine were associated with primary open-angle glaucoma in men, but not found in women [18]. As the previous studies reported a controversial relationship between IOP and testosterone [19,20], we are going to verify the hypothesis of whether IOP is associated with serum testosterone levels according to the severity of obesity in Korean men.

Thus, we aimed to investigate the relationship between IOP and serum testosterone by categorizing

subjects into normal, overweight, and obese according to the severity of obesity based on the anthropometric obesity indices. We investigate the association between IOP and testosterone after adjusting for age and anthropometric factors.

MATERIALS AND METHODS

1. Study design and subject

This was a retrospective study performed in accordance with the tenets of the Declaration of Helsinki. From January 1, 2012 to December 31, 2019, the mandatory electronic chart records were analyzed retrospectively for 3,949 healthy Korean men who were able to have their IOP, blood pressure, serum testosterone, and health factors were checked.

IOP was measured between 9 a.m. and 11 a.m. from Monday to Friday to minimize the effects of daily variation by adjusting mean IOP, and the procedure was repeated three times using non-contact tonometry (CT-80; Topcon, Tokyo, Japan). To avoid errors between the examiners, an experienced technician measured IOP without topical anesthesia. Fundus examination was conducted using a fundus camera (TRC-NW5S; Topcon) at 30° angle, including the optic nerve and the macula. We excluded glaucoma disease or retinal diseases, such as cup and disc (C/D) ratio 0.6 or higher, increase in the vertical C/D ratio, abnormal head of optic nerve, and hemorrhage of the optic nerve. The serum testosterone level was determined on the date of sampling using a commercially available radioimmunoassay kit. To check serum testosterone level, blood sampling was taken before noon.

Full physical examination was performed for height, weight, waist circumference, OI, BMI, and WtHR. Height and weight were measured through an automatic body measuring device with the patient wearing a light hospital gown and in standing position without wearing shoes. Waist circumference was measured at the end of a light exhalation with the legs spread 25 to 30 cm in an upright position. The measurement was made horizontally with just above the highest area of both iliac bones.

OI (modified Broca's index) was calculated as (actual body weight [kg]/standard body weight per height [kg]) \times 100, and derived as a standard body weight per height; (actual height-100) \times 0.9. BMI was calculated by weight (kg)/height² (m²). WtHR was calculated as waist

circumference (cm)/height (cm).

Mean arterial blood pressure (MAP) was calculated as (systolic blood pressure+2×diastolic blood pressure)/3. We classified the degree of patient obesity by various anthropometric obesity indices. In OI, 90 to 110 or less was defined as normal, 110 to 120 as overweight, and above 120 as obesity [17]. For BMI, only 18.5 to 25 kg/m² or less was normal, 25 to and 30 kg/m² or less was overweight and 30 kg/m² or more was obese [18]. For WtHR, only 0.51 or less was normal, 0.51 to 0.57 or less was overweight, and 0.57 or higher was divided in to three groups of obesity [19]. Statistical analysis was performed with one-way analysis of variance (ANOVA) for analyzing the differences of the MAP, IOP, and serum testosterone according to the severity of obesity; normal, overweight, and obesity in anthropometric obesity indices, and with regression analysis to determine the anthropometric obesity indices for the correlation between IOP and serum testosterone. In addition, Student's t-test, one-way ANOVA, and multiple regression analysis were used to identify the difference in the IOP according to serum testosterone levels. Statistical analysis was conducted using IBM SPSS ver. 19.0 for Windows (IBM Corp., Armonk, NY, USA).

2. Ethics statement

The present study protocol was reviewed and ap-

proved by the Institutional Review Board (IRB) of Pusan National University Hospital (Reg. No. 2003-008-088). The requirement for patient consent was waived by the IRB because of the retrospective nature of the study.

RESULTS

The average age of 3,949 healthy Korean men was 58.86±10.06 years, mean IOP was 14.40±2.61 mmHg, mean systolic blood pressure was 125.52±15.34 mmHg, mean diastolic blood pressure was 77.78±10.33 mmHg, mean blood pressure was 93.67±11.47 mmHg. The mean concentration of serum testosterone was 4.21±1.83 ng/mL, which was highest in under 30s, and decreased gradually until 60s. The serum testosterone level of over 70s was higher than that of patients in the groups of 50s and 60s. All anthropometric obesity indices tended to increase in their 40s and then decrease gradually (Table 1).

Table 2 shows the MAP, IOP, and serum testosterone according to the anthropometric obesity indices. In the classification as the OI, MAP was 91.49±11.43 mmHg, IOP was 14.25±2.62 mmHg, and serum testosterone was 4.48±1.91 ng/mL in the normal group. In the overweight group, MAP was 94.39±11.10 mmHg, IOP was 14.44±2.59 mmHg, and serum testosterone was 4.05±1.73

Table 1. Characteristics of patients with body, blood pressure, IOP, testosterone, and anthropometric obesity indices according to the age range of age

Characteristic	Age group (y)					Total
	Under 30s	40s	50s	60s	Over 70s	
Subject	155 (3.93)	555 (14.05)	1,237 (31.32)	1,453 (36.79)	549 (13.90)	3,949 (100)
Age (y)	36.08±3.25	45.07±2.89	55.35±2.86	63.78±2.80	74.10±3.88	58.86±10.06
Height (cm)	175.05±5.65	173.98±5.53	171.55±5.51	169.29±5.43	168.00±5.34	170.71±5.83
Weight (kg)	74.72±10.84	76.70±11.15	72.68±9.92	69.81±8.83	67.52±8.90	71.55±10.02
Waist (cm)	85.51±8.73	88.61±8.61	87.19±7.88	86.92±7.33	87.35±7.99	87.25±7.87
SBP (mmHg)	126.28±12.35	125.44±14.14	123.39±15.25	126.04±15.83	128.81±15.48	125.52±15.34
DBP (mmHg)	74.61±8.94	77.76±10.26	77.93±10.56	78.57±10.18	76.29±10.36	77.78±10.33
MAP (mmHg)	91.84±9.41	93.65±11.07	93.04±11.74	94.39±11.55	93.70±11.49	93.67±11.47
IOP (mmHg)	14.23±2.80	14.46±2.75	14.42±2.60	14.35±2.57	14.25±2.52	14.40±2.61
Testosterone (ng/mL)	4.52±1.83	4.28±1.86	4.17±1.78	4.17±1.85	4.27±1.83	4.21±1.83
Obesity index	110.72±14.72	115.26±14.84	112.93±12.95	112.02±11.89	110.45±12.83	112.49±12.98
BMI (kg/m ²)	24.36±3.23	25.31±3.25	24.66±2.83	24.32±2.57	23.90±2.74	24.51±2.83
WtHR	0.49±0.05	0.51±0.05	0.51±0.04	0.51±0.04	0.52±0.05	0.51±0.05

Values are presented as number (%) or mean± standard deviation.

IOP: intraocular pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial blood pressure, BMI: body mass index, WtHR: waist to height ratio.

Table 2. Comparative relationship among MAP, IOP, and testosterone according to the degree of obesity by anthropometric obesity indices

Index	Category	MAP (mmHg)	IOP (mmHg)	Testosterone (ng/mL)
Obesity index	Normal	91.49	14.25	4.48
	Overweight	94.39	14.44	4.05
	Obesity	96.85	14.58	3.88
	p-value	<0.001	0.019	<0.001
BMI (kg/m ²)	Normal	92.16	14.26	4.37
	Overweight	95.59	14.59	4.00
	Obesity	100.19	14.69	3.46
	p-value	<0.001	0.001	<0.001
WtHR	Normal	91.70	14.29	4.54
	Overweight	94.80	14.47	4.01
	Obesity	97.23	14.55	3.47
	p-value	<0.001	0.065	<0.001

One-way ANOVA was used to compare each group. MAP: mean arterial blood pressure, IOP: intraocular pressure, BMI: body mass index, WtHR: waist to height ratio.

ng/mL, respectively. Obesity groups showed 96.85±11.11 mmHg in MAP, 14.58±2.64 mmHg in IOP, and 3.88±1.64 ng/mL in testosterone, showing an increase as obesity intensifies. Actually, MAP and IOP increased significantly as the level of obesity increased, and testosterone significantly decreased ($p<0.001$, $p=0.019$, $p<0.001$). Regarding BMI, MAP gradually increased with obesity to 92.16±11.45 mmHg in normal, 95.59±10.98 mmHg in overweight, 100.19±11.15 mmHg in obesity. IOP has a similar tendency as MAP; 14.26±2.6 mmHg in normal, 14.59±2.6 mmHg in overweight, and 14.69±2.91 mmHg in obesity, but serum testosterone tended to decrease gradually to 4.37±1.89 ng/mL in normal, 4.00±1.67 ng/mL in overweight, and 3.46±1.51 ng/mL in obesity. In other words, the higher the obesity, the more significant was the increase in MAP and IOP and the lower was the testosterone level ($p<0.001$, $p=0.001$, $p<0.001$). The greater the obesity in WtHR, the greater was the increase in MAP, and the testosterone level tended to decrease ($p<0.001$ in all). In particular, IOP increased but no significant difference was shown.

Regarding the correlation among MAP, IOP, and testosterone, MAP-IOP and IOP-testosterone showed a positive correlation ($p<0.001$, $p=0.037$), but MAP-testosterone showed a significantly negative correlation ($p<0.001$) (Table 3).

A significantly positive correlation between IOP and testosterone, divided by normal, overweight, and obese in all anthropometric obesity indices, was found only

Table 3. The Pearson correlation coefficient between MAP, IOP, and serum testosterone level

	MAP	IOP	Testosterone
MAP	1		
IOP	0.105**	1	
Testosterone	-0.102**	0.033*	1

MAP: mean arterial blood pressure, IOP: intraocular pressure. * $p<0.05$, ** $p<0.001$.

Table 4. The Pearson correlation coefficient between testosterone and intraocular pressure according to the severity of obesity by anthropometric obesity indices

Anthropometric indice	Obesity index	BMI	WtHR
Normal	0.077**	0.060**	0.052*
Overweight	0.013	0.016	0.044
Obesity	0.027	-0.068	-0.034

One-way ANOVA was used to compare each group. BMI: body mass index, WtHR: waist to height ratio. * $p<0.05$, ** $p<0.01$.

in normal groups ($r=0.077$, $p<0.01$ in OI, $r=0.060$, $p<0.01$ in BMI, $r=0.052$, $p=0.028$ in WtHR), and there was no significant correlation between the overweight and obese groups (Table 4). Multiple regression analysis showed that testosterone was directly associated with IOP after adjusting for age and anthropometric obesity indices including OI, BMI, and WtHR (all $p<0.01$) (Table 5).

The serum testosterone level was compared in two groups based on 3.0 ng/mL of testosterone, which is normal limit of serum testosterone range. There was a significantly higher IOP of testosterone above 3.0 ng/mL (subject=2,833 [71%], mean IOP 14.56±1.35 mmHg) than that of testosterone <3.0 ng/mL (subject=1,116 [29%] and mean IOP 13.99±1.29 mmHg) (Fig. 1; $p<0.001$).

According to cut-off value of IOP, the serum testosterone was 3.96±1.44 ng/mL when the IOP was 21 mmHg or more, and 4.22±1.83 ng/mL when it was less than 21 mmHg. There was no statistically significant difference between the two groups ($p=0.230$).

DISCUSSION

This study showed that the relationship between IOP and serum testosterone in normal subjects was significantly correlated with that in overweight and obese men. In addition, among the obesity anthropometric index, OI and BMI have better indices than WtHR in

Table 5. The association between testosterone and IOP as each individual outcome in separate regression models after adjusting for age and obesity

Outcome variable	Covariate	β	95% CI	p-value	R ²
IOP	Testosterone	0.064	0.019–0.109	0.005	0.006
	Age	-0.007	-0.015–0.001	0.098	
	Obesity index	0.014	0.008–0.021	<0.001	
IOP	Testosterone	0.064	0.019–0.109	0.006	0.006
	Age	-0.006	-0.014–0.002	0.154	
	BMI	0.067	0.037–0.096	<0.001	
IOP	Testosterone	0.061	0.016–0.107	0.008	0.004
	Age	-0.010	-0.018–0.002	0.016	
	WtHR	0.053	1.198–4.882	0.001	

Multiple regression model was used to compare each group.

IOP: intraocular pressure, CI: confidence interval, BMI: body mass index, WtHR: waist to height ratio.

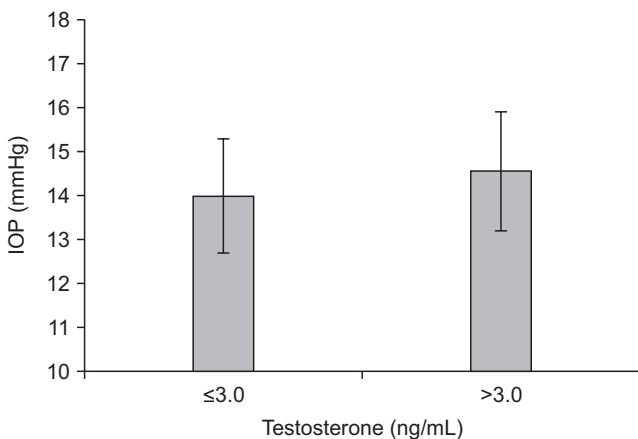


Fig. 1. Patients were categorized into two groups according to the serum testosterone level 3.0 ng/mL which is the normal lower limit of serum testosterone range. This graph showed that there was a significantly higher intraocular pressure (IOP) in patients with testosterone above 3.0 ng/mL (subject=2,833 [71%] mean IOP 14.56 mmHg) than in patients with testosterone below 3.0 ng/mL (subject=1,116 [29%] and mean IOP 13.99 mmHg) ($p < 0.001$ by independent t-test).

terms of predicting the association between IOP and serum testosterone. Health factors affecting IOP are well known for systemic diseases such as hypertension, diabetes, and obesity, related to aging and gender. Especially in obesity, they may exert a direct effect on IOP, because increased orbital pressure from excess fat may lead to high episcleral venous pressure and decreased outflow facility by the secretions of corticosteroids in obese peoples. The association between obesity and IOP adjusted by age, gender, or other health factors and their effects on IOP has been studied using anthropometric obesity indices. Previous studies showed a positive correlation with IOP and anthropometric indices, such as OI, BMI, and waist circumference [2,21].

Recently, the number of obese people has increased in Korea due to changes in dietary habits and lack of physical activity, obesity is becoming an important health issue. Therefore, we studied the correlation between IOP and anthropometric obesity indices in Korean men, including BMI, OI, and WtHR. Similar to previously published articles, this study showed that the association of MAP and IOP increased significantly as the severity of obesity increased, but testosterone decreased significantly [12,13]. However, there are few reports on the association between IOP and testosterone associated with the severity of obesity. This study was conducted to investigate the association between IOP and testosterone through each anthropometric OI by dividing degrees of obesity.

In the present study, the mean IOP was 14.4 ± 2.61 mmHg, consistent with the range of mean IOP published in previous studies [2,8]. Obesity tended to increase gradually until subjects were in their 40s and then decreases with aging. The mean IOP also rapidly increases in the 40s and 50s, indicating the highest level of IOP in their 40s of subjects, showing that blood pressure and obesity are closely related to IOP. A previous published report showed that a significant correlation between IOP and BMI, OI, and WtHR [2]. Moreover, our results additionally indicate that IOP is positive association with the serum testosterone level in men of normal weight, not those in the obese group.

In various cross-sectional studies on aging and IOP, a positive relationship was observed between them in Westerners [2,8], whereas a negative relationship was found in Eastern populations [9,22]. In this study, IOP tends to increase and decrease in subjects in their 40s,

similar to the previously mentioned negative correlation among Eastern subjects. It is known to be due to differences in race, national, environmental and genetic factors of subjects [22]. Regarding obesity, many domestic and foreign studies have shown the significant relationship between anthropometric obesity indices and IOP [1-10]. In this study, the mean IOP showed significant differences among each group, according to anthropometric obesity indices, such as OI ($p=0.019$) and BMI ($p=0.001$).

Testosterone reduces activity of eNOS in the trabecular meshwork to lower the outflow capacity to increase IOP [9,23]. In animal study conducted on both male and female rats, DHTS decreases NOS activity, NOS mRNA expression, and the number of NOS+ neurons in the central nervous system. Generally, testosterone increase NOS activity in some areas of body and the brain, whereas it would decrease NOS in other areas where 5α -reductase is present [24]. In experiments conducted on male Dutch-belted rabbits, IOP were also elevated when the serum testosterone level was elevated by sexual development [25]. Gonzales also reported that male rodents have increased vascular tone in the middle cerebral arteries compared with female rodents [26]. This could explain the discrepancies observed in the actions of testosterone in regulating NOS activity in different organs of the body [24]. Overall, androgen receptor mRNA and 5α -reductase mRNA were found in men's ocular tissue as well as in women's ocular tissue [27,28]. Therefore, the possibility that testosterone may be converted to DHTS not only in women but also in men cannot be excluded. Actually, DHTS converted from testosterone by 5α -reductase in the trabecular meshwork may increase IOP by reduction of eNOS activity and suppression of the outflow facility [15].

In recent years, the westernized dietary habits have led to an increase in the obese population, which may be associated with hypogonadism due to a decrease in testosterone [12-14]. In this study, testosterone was also measured with the mean concentration of 4.21 ng/mL, the highest peak exists in their under 30s of subjects, and showed a gradual decrease until 60s. The highest anthropometric obesity indices were achieved in 40s of subjects and gradually decreased. This means that the degree of testosterone diurnal variation decreased by age. Although the difference of correlation between IOP and testosterone according to the severity of obesity is unclear, it is evident that testosterone

has particular influence on ocular blood flow, aqueous humor dynamics and IOP [14]. We also found that the testosterone level was directly associated with IOP after adjusting for age and anthropometric obesity indices in this study. As the OI increases, the IOP rises, but testosterone decreases in the high OI. It is thought that the relationship between IOP and testosterone was affected by obesity and offset by each other. Thus, the control of weight loss from obese in healthy men can alleviate the lack of testosterone in the body [12,23].

This study also found that IOP of testosterone above 3.0 ng/mL was significantly higher than that of testosterone less than 3.0 ng/mL, which was the therapeutic criteria of testosterone replacement therapy (TRT) [14]. The overdose of testosterone therapy can cause an increase in IOP due to the positive correlation of IOP-testosterone in normal-weight healthy men as shown by this study. In a previous study, increased IOP and ciliochoroidal effusion syndrome with chorioretinopathy due to using topical testosterone gel for 6 months was reported [29]. Prospective study of the correlation between the testosterone level and IOP is required to eliminate the bias variation which is affect serum testosterone level in men.

Ocular hypertension is defined as the IOP is higher than 21 mmHg, and there is no evidence of glaucomatous findings in the visual field and cupping of optic nerve. However, ocular hypertension is known as the most common risk factor for open-angle glaucoma and metabolic syndrome. In this study, there was no significant difference in concentration of testosterone between the two groups, with IOP of 21 mmHg or higher was 3.96 ± 1.44 ng/mL and IOP of 21 mmHg below was 4.22 ± 1.83 ng/mL of testosterone. According to this study, as the correlation of IOP-testosterone has a significant positive relationship, it is thought that a wider epidemiological investigation on testosterone levels in the case of ocular hypertension or glaucoma is needed.

There is no research on the direct association between IOP and the concentration of serum testosterone associated with the severity of obesity. Thus, we evaluated the relationship between IOP and serum testosterone by categorizing subjects into the severity of obesity by the anthropometric obesity indices. There is a positive correlation between IOP and testosterone in healthy Korean men. A wider epidemiological study, including oriental and western countries on the relationship between IOP and testosterone is thought to be

necessary to study the possibility of open angle glaucoma related to increasing IOP.

CONCLUSIONS

The correlation of IOP-testosterone has a significant positive relationship, especially in cases of healthy men with normal weight based on anthropometric obesity indices, such as OI or BMI. A wider epidemiological study on the relationship between IOP and testosterone should be conducted to evaluate the effect on increasing IOP.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: JSL. Data curation: JHK. Formal analysis: JHK. Supervision: JHS, HJP. Visualization: YJJ. Writing – original draft: JSL, MHL. Writing – review & editing: JSL, YJJ, MHL.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at <https://doi.org/10.7910/DVN/YP1PH1>.

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