Association of intraocular pressure with the metabolic syndrome and novel cardiometabolic risk factors

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CLINICAL STUDY

Abstract

Background and aims This study aimed to investigate the association of intraocular pressure (IOP) with the metabolic syndrome and other emerging cardiometabolic risk factors.

Methods A total of 1112 participants undergoing a health check-up in a community hospital were recruited. All participants underwent ophthalmological examination including IOP measurement.

Results Participants with metabolic syndrome had significantly higher IOP than those without metabolic syndrome (mean IOP $\pm$ SD: 15.07 ± 2.74 vs 14.29 ± 2.72 mm Hg, $P = 2 \times 10^{-4}$). Each additional component of the metabolic syndrome was associated with a mean increase in IOP of 0.33 mm Hg (95% confidence interval: 0.18–0.48, trend $P < 0.0001$). Other insulin resistance-related features, including hepatic steatosis, increased left ventricular mass, and proteinuria, were also associated with IOP ($P < 0.0001$, 0.002, and 0.01, respectively). However, we did not find significant association of plasma apolipoprotein A, apolipoprotein B1, homocysteine, or highly sensitive C-reactive protein levels with IOP. IOP was also not associated with measures of subclinical atherosclerosis including brachial–ankle pulse wave velocity, ankle–brachial index, and vertebral artery flow.

Conclusion Metabolic syndrome and other insulin resistance-related features, including hepatic steatosis, increased left ventricular mass, and proteinuria, are strongly associated with IOP. *Eye* (2010) 24, 1037–1043; doi:10.1038/eye.2009.247; published online 9 October 2009

Keywords: intraocular pressure; metabolic syndrome; hepatic steatosis; left ventricular mass; proteinuria; risk factor

Introduction

Intraocular pressure (IOP) is the only known modifiable risk factor for primary open-angle glaucoma (POAG).^{1,2} IOP is determined by the balance between aqueous humour secretion and outflow.³ However, the pathophysiology of elevated IOP is still not fully understood.³ Many cross-sectional and longitudinal epidemiological studies have reported associations of elevated IOP with cardiometabolic risk factors, such as type II diabetes, systemic hypertension, and concurrent atherosclerotic disease.^{4–21} These findings suggest a common underlying mechanism linking elevated IOP to various related cardiometabolic risk factors. The metabolic syndrome, an integrated concept for several commonly clustered disorders, including abdominal obesity, dyslipidemia, elevated blood pressures, and impaired fasting glucose, has been proposed as the ‘common soil’ for type II diabetes and atherosclerotic diseases.^{22,23} Therefore, we hypothesised that metabolic syndrome or other related cardiometabolic risk factors might be involved in the pathogenesis of ocular hypertension. In this study, we analysed the relationships between IOP and the metabolic syndrome and several emerging cardiometabolic risk factors in a cross-sectional study.²⁴ The association of IOP with surrogate measures of atherosclerosis, including brachial–ankle pulse wave velocity (PWV), ankle–brachial index (ABI), and vertebral artery flow, was also explored.^{25,26}

Subjects and methods

Study participants

We retrospectively analysed the clinical data of 1112 consecutive participants undergoing a health check-up at National Taiwan University

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Hospital Yun-Lin Branch, a community hospital in rural Taiwan from August 2006 to March 2008. This programme is a multi-faceted health check-up including history taking, physical examination, and multi-systemic, non-invasive or semi-invasive laboratory and image examinations, and is self-paid by the examinees. After exclusion of participants with past history of glaucoma or diabetic retinopathy, a total of 1044 participants were analysed. Body weight and waist circumference were measured with subjects wearing light clothes and in bare feet. Blood pressure was measured using mercury sphygmomanometer to the nearest 2 mm Hg. Trained nurses took three separate readings at 1-min intervals. Hypertension was defined as a systolic blood pressure (SBP) of 140 mm Hg and above and a diastolic blood pressure (DBP) of 90 mm Hg and above, or pharmacological treatment for a previously diagnosed hypertension. This study was approved by the institutional review board of National Taiwan University Hospital.

Ophthalmological examination

All participants underwent ophthalmological examination including best-corrected visual acuity, refraction, IOP measurement by non-contact tonometry (Topcon CT80, Topcon, Tokyo, Japan), and dilated fundus examination. The IOP was measured on the centre of cornea for three consecutive times for each eye by a trained nurse who was blind to other health information of participants. All ophthalmic examination was performed between 0800 hours and 1100 hours. The mean IOP was calculated for each eye. The average IOP of both eyes was used for analysis. Ocular hypertension was defined as IOP ≥ 20 mm Hg in one or both eyes.

Laboratory measurements

A venous blood sample was collected in the morning after overnight fasting. Fasting glucose, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid, and highly sensitive C-reactive protein levels were analysed using an automatic analyser (Toshiba TBA 120FR, Toshiba Medical System Co, Tokyo, Japan). The metabolic syndrome was defined according to the National Cholesterol Education Program Third Adult Treatment Panel Guidelines (NCEP ATP III) with modification for Asian populations.^{27,28} The five components of the metabolic syndrome included waist circumference > 90 cm in men or > 80 cm in women, triglycerides ≥ 150 mg per 100 ml, HDL-C < 40 mg per 100 ml in men or < 50 mg per 100 ml in women, blood pressure $\geq 130/ \geq 85$ mm Hg, and fasting glucose ≥ 100 mg per 100 ml. The metabolic syndrome was defined as having at least

three of the five components.^{27,28} Plasma homocysteine levels were determined by an automated immunoassay analyser (Immulite 2000, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma fibrinogen levels were measured by an automated blood coagulation analyser (CA-500, Sysmex Co, Kobe, Japan). Plasma apolipoprotein A1 and apolipoprotein B levels were measured by immunoturbidimetric immunoassay (Dade Behring Dimension RxL System, Dade Behring Co, Tokyo, Japan). Dipstick urinalysis was performed on fresh mid-stream urine collected in the morning. The results of the urine test were semi-quantitatively interpreted as negative, trace, 1+, 2+, 3+, and 4+. Ultrasonography of the abdomen was performed by gastroenterology specialists. Hepatic steatosis was diagnosed by characteristic echo patterns, according to the conventional criteria (that is, evidence of diffuse hyperechogenicity of the liver relative to the kidney, ultrasound beam attenuation, and poor visualisation of intrahepatic structures). Brachial-ankle PWV and ABI were measured using an automated ABI/PWV analyser (model BP-203 PRE II, Colin Medical Technology, Komaki, Japan). Bilateral arm and ankle blood pressure, and pulse volumes of the brachial and posterior tibial arteries were recorded. Brachial-ankle PWV was obtained by the equation, as described previously.²⁵ The averages of bilateral brachial-ankle PWV and ABI were used for analyses. Total vertebral artery flow was assessed by colour Doppler ultrasound scan (HD11XE, Philips Medical System, Hamburg, Germany) performed by a trained technician. Echocardiographic ultrasound (Vivid 7 Dimension, General Electric, Milwaukee, WI, USA) was performed by cardiologists according to the criteria recommended by the American Society of Echocardiography.²⁹ Left ventricular mass (g) was calculated as $0.8 \times \{1.04 \times [(\text{left ventricular wall inner diameter} + \text{interventricular septum thickness} + \text{left ventricular posterior wall thickness})^3 - (\text{left ventricular inner diameter})^3]\} + 0.6$.^{30,31}

Statistical analysis

Discrete data were presented as frequencies and percentages, and continuous variables as means and standard deviation (SD). Variables that were not distributed normally were logarithmically transformed to approximate normal distribution before analysis. Student's *t*-test was used to compare continuous traits between participants without and with the metabolic syndrome. Logistic regression was used to estimate the risk of ocular hypertension associated with the metabolic syndrome. Univariate linear regression was used to estimate the association of IOP with individual metabolic trait. The effect size of unit change in individual

metabolic trait on IOP was also estimated. Multivariate linear regression with stepwise selection was used to develop models predicting IOP. In model 1, all variables that were significantly associated with IOP in univariate analyses were entered into stepwise selection. In model 2, the same variables were entered into the analyses except that the five component of the metabolic syndrome were replaced by the presence or absence of the metabolic syndrome. In model 3, the five components of the metabolic syndrome were replaced by the number of components (0–5). The *P*-values for entry and removal were 0.05 and 0.05, respectively. A two-tailed *P*-value <0.05 was considered as statistically significant.

Results

Clinical characteristics of the study participants

The demographic and biochemical characteristics of study participants according to the diagnosis of metabolic syndrome are shown in Table 1. The mean IOP was 14.29 ± 2.72 mm Hg in participants without the metabolic syndrome and 15.07 ± 2.74 mm Hg in those with the metabolic syndrome. The prevalence of ocular

hypertension was 2.98 and 5.56% in participants without and with the metabolic syndrome, respectively.

The association of IOP with the metabolic syndrome and related metabolic parameters

In univariate regression analysis, male sex, current smoking, body mass index, waist circumference, SBP, DBP, fasting glucose, triglycerides, uric acid, and fibrinogen levels were positively associated with IOP, whereas age and HDL-C levels were negatively associated with IOP (Table 2). Stepwise multivariate regression analysis showed that age, male sex, DBP, fasting plasma glucose, and triglyceride levels were independently associated with IOP (Table 3, model 1).

The metabolic syndrome was associated with an increase of IOP of 0.78 mm Hg (95% confidence interval (CI): 0.37–1.19, $P = 2 \times 10^{-4}$, Table 2). The difference remained significant in stepwise multivariate regression model (adjusted $P = 0.002$, Table 3, model 2). Each additional component of the metabolic syndrome was associated with an increase in IOP of 0.33 mm Hg (95% CI: 0.18–0.48, trend $P < 0.0001$, Figure 1). The linear trend

Table 1 Clinical characteristics of study participants according to diagnosis of the metabolic syndrome

	N	Without metabolic syndrome	With metabolic syndrome	P-values	Reference values
		804	240		
Age (years)	1044	49.53 ± 11.53	55.23 ± 10.71	<0.0001	
Male sex (%)	1044	54.98	69.17	<0.0001	
Current smoker (%)	1044	16.54	26.25	0.0007	
Body mass index (kg/m ²)	1024	23.49 ± 3.10	27.41 ± 9.85	<0.0001	18.5–24
Waist circumference (cm)	1000	77.63 ± 10.43	88.94 ± 9.63	<0.0001	Male: <90 Female: <80
Systolic blood pressure (mm Hg)	1035	118.9 ± 18.27	134.9 ± 18.23	<0.0001	<130
Diastolic blood pressure (mm Hg)	1035	75.90 ± 12.31	86.24 ± 11.55	<0.0001	<85
Fasting glucose (mg/dl)	1042	90.42 ± 15.74	118.9 ± 41.61	<0.0001	60–100
HDL-C (mmol/l)	885	1.27 ± 0.29	1.03 ± 0.20	<0.0001	Male: >1.04 Female: >1.30
LDL-C (mmol/l)	1024	3.49 ± 1.01	3.53 ± 1.15	0.58	<3.34
Triglycerides (mmol/l)	1042	1.28 ± 0.83	2.57 ± 1.23	<0.0001	0.34–2.26
Uric acid (μmol/l)	1030	343.3 ± 95.2	402.2 ± 108.3	<0.0001	179–476
Apolipoprotein A1 (g/l)	710	1.36 ± 0.19	1.25 ± 0.20	<0.0001	1.19–2.40
Apolipoprotein B (g/l)	710	0.99 ± 0.24	1.12 ± 0.34	<0.0001	0.52–1.63
Homocysteine (μmol/l)	667	8.16 ± 3.15	9.02 ± 3.65	<0.01	4.4–10.8
Fibrinogen (g/l)	616	3.03 ± 0.69	3.04 ± 0.58	0.98	2.33–4.96
hsCRP (mg/l)	770	0.25 ± 0.75	0.28 ± 0.54	0.56	0.2–3.0
Left ventricular mass (g)	814	155.8 ± 45.66	193.8 ± 49.35	<0.0001	Sex and body-surface dependent
Proteinuria (%)	1037	1.74	3.18	<0.0001	
Hepatic steatosis (%)	1044	40.92	73.33	<0.0001	
Ankle-brachial index	757	1.14 ± 0.77	1.16 ± 0.83	0.04	0.9–1.3
Brachial-ankle pulse wave velocity (cm/s)	767	1391.6 ± 298.8	1569.1 ± 307.2	<0.0001	Age dependent
Total vertebral artery flow (cm/s)	764	173.7 ± 80.6	168.8 ± 88.93	0.48	>100
Intraocular pressure (mm Hg)	926	14.29 ± 2.72	15.07 ± 2.74	0.0002	10–20
Ocular hypertension (%)	926	2.98	5.56	0.07	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein. Data was presented as mean $\pm$ SD.

Table 2 Univariate regression analysis for association with intraocular pressure

	Effect size (95% CI)	P-value
<i>Traditional cardiometabolic risk factors</i>		
Age (per decade, years)	-0.4 (-0.55, -0.25)	<0.0001
Male sex	0.76 (0.41, 1.11)	<0.0001
Current smoking	0.62 (0.19, 1.05)	0.005
Body mass index (per SD)	0.48 (0.30, 0.66)	<0.0001
Waist circumference (per SD)	0.37 (0.19, 0.55)	<0.0001
Systolic blood pressure (per SD)	0.29 (0.11, 0.47)	0.001
Diastolic blood pressure (per SD)	0.45 (0.27, 0.63)	<0.0001
Fasting glucose (per SD)	0.35 (0.19, 0.51)	<0.0001
HDL-C (per SD)	-0.2 (-0.40, -0.04)	0.03
LDL-C (per SD)	0.045 (-0.13, 0.22)	0.64
Triglycerides (per SD)	0.43 (0.25, 0.61)	<0.0001
<i>Novel cardiometabolic risk factors</i>		
Uric acid (per SD)	0.25 (0.07, 0.43)	0.003
Apolipoprotein A1 (per SD)	-0.09 (-0.31, 0.13)	0.41
Apolipoprotein B (per SD)	0.2 (-0.02, 0.42)	0.07
Homocysteine (per SD)	0.05 (-0.17, 0.27)	0.63
Fibrinogen (per SD)	0.27 (0.03, 0.51)	0.02
hsCRP (per SD)	0.11 (-0.13, 0.35)	0.79
<i>Insulin resistance-associated features</i>		
Left ventricular mass (per SD)	0.3 (0.10, 0.50)	0.002
Proteinuria	0.61 (-0.57, 1.79)	0.01
Hepatic steatosis	0.72 (0.37, 1.07)	<0.0001
Metabolic syndrome	0.78 (0.37, 1.19)	0.0002
<i>Measures of subclinical atherosclerosis</i>		
Ankle-brachial index (per SD)	-0.03 (-0.25, 0.19)	0.79
Brachial-ankle pulse wave velocity (per SD)	0.002 (-0.21, 0.22)	0.99
Vertebral artery flow (per SD)	-0.15 (-0.04, 0.34)	0.12

Abbreviations: CI, confidence interval; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

The effect size indicates the change of intraocular pressure associated with change of each metabolic trait.

remained significant in stepwise multivariate regression (adjusted $P = 0.002$, Table 3, model 3). The linear trend was also significant after exclusion of participants with elevated blood pressure ($P = 0.0017$) or participants with elevated blood pressure and fasting glucose ($P = 0.01$). The metabolic syndrome was also associated with a trend of increased risk of ocular hypertension (odds ratio: 1.92, 95% CI: 0.93–3.96, $P = 0.07$).

The association of IOP with hepatic steatosis, left ventricular mass, and proteinuria

Other insulin resistance-associated features, including hepatic steatosis, left ventricular hypertrophy, and proteinuria, have been proved to be risk factors of cardiovascular diseases.^{32–34} Interestingly, we found significant associations of hepatic steatosis, left ventricular mass, and proteinuria with IOP ($P < 0.0001$, $P = 0.002$, and 0.01, respectively). Participants with hepatic steatosis had significantly higher IOP than those without hepatic steatosis (mean IOP $\pm$ SD: 14.84 ± 2.64 vs

Table 3 Stepwise multivariate regression analysis for association with intraocular pressure

	Model 1		Model 2		Model 3	
	Effect size (95% CI)	P-value	Effect size (95% CI)	P-value	Effect size (95% CI)	P-value
Age (per decade, years)	-0.62 (-0.80, -0.44)	<0.0001	-0.47 (-0.67, -0.27)	<0.0001	-0.68 (-0.42, -0.94)	<0.0001
Male sex	0.49 (0.06, 0.92)	0.02	0.97 (0.52, 1.42)	<0.0001	0.93 (0.38, 1.47)	0.001
Diastolic blood pressure (per SD)	0.55 (0.30, 0.80)	<0.0001	0.81 (0.30, 1.32)	0.002	0.34 (0.12, 0.56)	0.002
Fasting glucose (per SD)	0.29 (0.07, 0.51)	0.008				
Triglycerides (per SD)	0.23 (0.01, 0.45)	0.04

Figure 1 Mean intraocular pressure according to numbers of component of the metabolic syndrome. Data was expressed as mean $\pm$ SE.

14.12 $\pm$ 2.88 mm Hg, $P < 0.0001$). IOP was also positively associated with plasma alanine transaminase (ALT) levels ($P = 0.01$) and AST (aspartate aminotransferase) to ALT ratio ($P = 0.0003$), both are indicators of hepatic steatosis. The association remained significant by adjustment of age and sex. The association of IOP with hepatic steatosis and left ventricular mass was attenuated by adjustment for the metabolic syndrome (adjusted $P = 0.004$ and 0.03 , respectively). The association of IOP with proteinuria was abolished by adjustment for the metabolic syndrome (adjusted $P = 0.11$).

The association of IOP with surrogate measures of arterial atherosclerosis

We did not find any significant association of IOP with ABI ($P = 0.79$), brachial-ankle PMV ($P = 0.99$), or with vertebral artery blood flow ($P = 0.12$).

Discussion

In this study, we found that the metabolic syndrome and its components were linearly and independently associated with IOP. Other insulin resistance-related features, including hepatic steatosis, left ventricular hypertrophy, and proteinuria, were also associated with IOP. The data implied that the metabolic syndrome or insulin resistance might be involved in the pathogenesis of ocular hypertension. Consistent with our findings, Oh *et al*³⁴ recently reported a significant association between IOP and the metabolic syndrome in the Korean population. The mean increase of IOP associated with the metabolic syndrome was similar between the two studies (0.78 mm Hg in our study *vs* 0.86 mm Hg reported by Oh *et al*).³⁴ In both studies, significant linear associations were found between IOP and the number of components

of the metabolic syndrome.³⁴ Oh *et al* found a significant association between IOP and insulin sensitivity index including homoeostasis model assessment of insulin resistance and McAuley index. We also found strong associations between IOP and several insulin resistance traits including hepatic steatosis, increased left ventricular mass, and proteinuria. The independent replication by our study confirmed the association of the metabolic syndrome or related metabolic features with IOP. These results strongly indicate a link between IOP and insulin resistance.

The mechanism by which the metabolic syndrome is associated with IOP is currently unknown. However, recent research has revealed some potential pathophysiological links. For example, sympathetic hyperactivation is a common feature of obesity, hypertension, and insulin resistance.^{35,36} Stimulation of the ocular sympathetic nerve increases IOP, whereas topical β -adrenergic antagonist reduces IOP.³⁷ β -adrenergic receptor polymorphism is also associated with obesity, insulin resistance, IOP, and POAG.^{36,38} Another possible link is the endocannabinoid pathway, a pivotal pathway controlling appetite and energy homoeostasis.³⁹ Endocannabinoid overactivity contributes to the development of abdominal obesity, dyslipidemia, hyperglycaemia, and hepatic lipogenesis.³⁹ Interestingly, endocannabinoid receptors were also expressed in various eye tissues including the ciliary body, corneal epithelium, trabecular meshwork, and the canal of Schlem.⁴⁰ Endocannabinoids such as arachidonylethanolamide regulate aqueous outflow in the trabecular meshwork and influence IOP in rodents when administered intravenously or topically.⁴⁰ Similarly, the aquaporins, a family of small membrane proteins that transport water and small molecules such as glycerols, are also expressed in a variety of human tissue including the corneal endothelium, ciliary epithelium, trabecular meshwork, choroid plexus, adipose tissue, liver, and pancreas.⁴¹ Aquaporins have been shown to increase aqueous fluid secretion across the ciliary epithelium and regulate IOP.⁴¹ Unexpectedly, aquaporin-knockout mice were obese and developed severe insulin resistance.^{42,43} Sympathetic hyperactivation, the endocannabinoid pathway, and the aquaporins are possible links between the metabolic syndrome and IOP.

Our findings may have potential clinical and public health implications. The prevalence of the metabolic syndrome is rapidly increasing worldwide because of sedentary lifestyles. If the causal relationship between the metabolic syndrome and IOP is proven true, the epidemic of the metabolic syndrome will have a great impact on the incidence of POAG. Amelioration of the metabolic syndrome by lifestyle intervention may have therapeutic potential for the IOP lowering. However,

further studies are required to clarify the causal relationship between insulin resistance and IOP.

The strength of our study includes a comprehensive investigation of cardiometabolic risk factors and the unbiased measurement of IOP. Previous hospital-based case-control studies tend to overestimate the proportion of glaucoma patients who also have type II diabetes or systemic hypertension, because such patients are more likely to receive eye examination. In our study, eye examination and IOP measurements were routinely performed so that such selection bias could be reduced.

Our study has several limitations. First, this is a cross-sectional study. Therefore, the causal relationship could not be determined. Further intervention studies will be needed to address whether ameliorating the metabolic syndrome prevents ocular hypertension and POAG. Second, we did not measure parameters of insulin resistance such as insulin sensitivity index by oral glucose tolerance tests or clamp study. Therefore, the association between insulin resistance and IOP could not be analysed. Third, non-contact tonometry is not as reliable as the Goldmann applanation tonometry and is affected by central corneal thickness (CCT). The association with IOP would have been more accurate if the CCT was measured and included in the analyses.

In summary, we have shown that the metabolic syndrome and its components are associated with IOP. The effect of the metabolic syndrome on IOP is evident early in the pre-disease stage. Furthermore, other insulin resistance-associated features such as hepatic steatosis, left ventricular hypertrophy, and proteinuria were also associated with IOP. These data highlighted a potential role of metabolic syndrome or insulin resistance in ocular hypertension.

Summary

What was known before

- Elevated intraocular pressure has been linked to type II diabetes, hypertension, and obesity.

What this study adds

- Metabolic syndrome and other insulin resistance-related features, including fatty liver, proteinuria, and left ventricular hypertrophy are associated with elevated intraocular pressure.

Conflict of interest

The authors declare no conflict of interest.

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