Insulin Resistance Is a Risk Factor for Increased Intraocular Pressure: The Hisayama Study

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Purpose. To investigate association of the homeostasis model assessment of insulin resistance (HOMA-IR), a surrogate index of insulin resistance, with IOP in a general Japanese population.

Methods. In 2007, a total of 3119 Japanese community-dwellers, aged 40 years or older, underwent eye examinations, including IOP measurement with a noncontact tonometer. Of these, 2254 residents participated in this study. Fasting serum glucose and plasma insulin were measured to determine the HOMA-IR. The association of HOMA-IR with IOP was assessed using a linear regression model, adjusted for age and possible risk factors that can elevate IOP.

Results. The mean IOP ± SD was 13.7 ± 2.7 mm Hg in the right eye and 13.6 ± 2.7 mm Hg in the left eye. After adjusting for age, sex, systolic blood pressure, diabetes, total cholesterol, high-density lipoprotein cholesterol, body mass index, waist circumference, smoking habits, alcohol intake, and regular exercise, increased HOMA-IR levels were significantly associated with increasing IOP ($P < 0.05$). In the subgroup analyses based on the presence or absence of possible confounding risk factors, there was no evidence of heterogeneity between all subgroups (P for heterogeneity > 0.08).

Conclusions. The HOMA-IR is independently associated with elevated IOP levels after adjustment for confounding factors.

Keywords: intraocular pressure, the homeostasis model assessment of insulin resistance (HOMA-IR), population-based study, cohort study

Intraocular pressure (IOP) is one of the physiologic characteristics of maintaining homeostasis in the eye. As reported in several population-based studies, elevated IOP is a major risk factor for the development of glaucoma,[1–3] which is a significant cause of visual impairment throughout the world.[4] Moreover, lowering the elevated levels of IOP can reduce the risk of glaucoma.[5]

Although IOP is locally determined by ocular factors, it is influenced by systemic factors as well.[1–3,6] Several epidemiologic studies have demonstrated that known cardiovascular risk factors, namely obesity, hypertension, diabetes, and dyslipidemia, are associated with increased IOP.[6–10] Insulin resistance caused by a high-fat diet[11] and obesity[12] can induce hypertension,[13] impaired glucose tolerance,[12] dyslipidemia,[13] and subsequent cardiovascular disease.[14,15] Some hospital-based studies have shown that insulin resistance is a metabolic factor for increasing IOP.[7–9] Because insulin resistance has recently become more common in Japan,[16] it is worthwhile to clarify the association between insulin resistance and IOP. Herein, we investigated the association of the homeostasis model assessment of insulin resistance (HOMA-IR), which is a surrogate index of insulin resistance,[17] with IOP in a general Japanese population. We also examined how potential confounding factors exert an influence on IOP.

Methods

Study Population

The Hisayama Study is an ongoing, long-term cohort study on cardiovascular disease and its risk factors in the town of Hisayama,[18,19] adjoining the city of Fukuoka, a metropolitan area in southern Japan. As a part of the overall study, an epidemiologic study of eye disease among residents of the town has been under way since 1998.[20] In 2007, 3119 of the 4298 residents (72.6%) aged 40 years or older consented to participate and underwent an ophthalmic examination for the present study.

Subjects were excluded for the following reasons: missing IOP values ($n = 201$), use of topical IOP-lowering medications ($n = 133$), and previous ocular surgery ($n = 372$). Thus, 2413 subjects remained whose IOP was not medically or surgically influenced. Among these subjects, on the day of assessment some were excluded for the following reasons: already had breakfast ($n = 11$), taking oral hypoglycemic agents ($n = 139$), and taking insulin therapy for diabetes ($n = 9$). Finally, 2254 subjects (1005 men and 1249 women) were enrolled in the present study.

Table 1. Characteristics of Subjects by HOMA-IR Levels, The Hisayama Study, 2007

Variable	HOMA-IR Quartile Level, $n = 2254$				
	Quartile 1, $n = 563$	Quartile 2, $n = 564$	Quartile 3, $n = 564$	Quartile 4, $n = 563$	*P* for Trend
Age, y	61 ± 12	61 ± 11	60 ± 11	60 ± 11	0.21
Men, %	44.6	44.5	44.7	44.6	0.98
Fasting plasma glucose, mg/dL	95 ± 11	99 ± 10	103 ± 14	111 ± 21	<0.0001
Fasting plasma insulin, pg/dL	2.66 (1.37–5.19)	4.53 (3.31–6.19)	6.30 (4.25–9.32)	10.70 (5.49–20.83)	<0.0001
Diabetes, %	3.6	4.4	8.3	21.0	<0.0001
Systolic blood pressure, mm Hg	124 ± 19	127 ± 18	132 ± 18	136 ± 18	<0.0001
Diastolic blood pressure, mm Hg	76 ± 11	78 ± 10	80 ± 10	83 ± 10	<0.0001
Hypertension, %	32.9	37.4	45.7	58.4	<0.0001
Total cholesterol, mg/dL	208 ± 36	210 ± 34	214 ± 37	215 ± 37	0.0001
HDL-cholesterol, mg/dL	76 ± 19	68 ± 18	66 ± 16	59 ± 15	<0.0001
BMI, kg/m^2	20.8 ± 2.4	22.5 ± 2.6	23.5 ± 2.8	25.7 ± 3.4	<0.0001
Waist circumference, cm	79 ± 7	83 ± 8	86 ± 8	91 ± 9	<0.0001
Current smoking, %	24.5	24.8	21.3	19.7	0.02
Current drinking, %	55.5	52.3	50.4	46.9	0.003
Regular exercise, %	11.6	12.8	12.1	11.6	0.87

Values are given as means ± SDs or as percentages. Geometric means and 95% prediction intervals are shown for fasting insulin due to its skewed distributions. The HOMA-IR levels were divided into sex-specific quartiles: men, Q1, ≤0.88; Q2, 0.89 to 1.31; Q3, 1.32 to 2.02; Q3, 1.32–2.02; and Q4, ≥2.03; women, Q1, ≤0.89; Q2, 0.90 to 1.29; Q3, 1.30 to 1.93; and Q4, ≥1.94.

Clinical Evaluation and Laboratory Measurements

Each participant underwent a comprehensive ophthalmic examination using methods previously described.[20] The IOP was measured three consecutive times with a noncontact tonometer using automatic air-puff control on the center of the cornea (Nidek NT-4000; Nidek Co., Ltd., Gamagori, Japan), and the mean value for each eye determined. We used the mean IOP values of both eyes of each subject in the analysis. The IOPs were measured between 8 and 11 AM to reduce the small variation caused by circadian rhythm.

To determine plasma insulin and serum glucose levels, blood samples were collected from the antecubital vein after an overnight fast and analyzed within 24 hours. Plasma glucose was measured using the glucose-oxidase method, and serum insulin levels were determined by a commercial double-antibody solid-phase radioimmunoassay (Phadeseph Insulin; Pharmacia Diagnostics AB, Uppsala, Sweden). After the fasting blood samples were taken, a 75-g oral glucose tolerance test was performed between 8 AM and 10:30 AM. At 120 minutes after ingestion of the solution, a blood sample was obtained to determine postloading plasma glucose levels. These specimens were analyzed within 24 hours. Insulin resistance was estimated by HOMA-IR values, calculated as follows[17]:

$$\textit{fasting plasma glucose}\ (\text{mg/dL}) \times \textit{fasting serum insulin}\ (\mu\text{U/mL})/405.$$

Diabetes was defined as fasting plasma glucose of 7.0 mM (126 mg/dL) or higher and 2-hour postload glucose of 11.1 mM (200 mg/dL) or higher.

Blood pressure was measured three times after the subject had rested for 5 or more minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure 90 mm Hg or higher, or current use of antihypertensive medication. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically. Hypercholesterolemia was defined as total cholesterol levels of 5.7 mM (220 mg/dL) or higher. Reduced HDL cholesterol was defined as HDL cholesterol levels of lower than 1.03 mM (40 mg/dL) in men and lower than 1.29 mM (50 mg/dL) in women. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI) (kg/m^2) was calculated. Waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire. Smoking habits and alcohol intake were classified into either current habitual use or not, and those subjects who engaged in sports or other forms of exertion three or more times per week during their leisure time were designated the regular exercise group.

Statistical Analysis

The SAS software package (version 9.3; SAS Institute, Inc., Cary, NC, USA) was used to perform all statistical analyses. The HOMA-IR values were treated as a continuous variable and fasting plasma insulin levels were transformed into logarithms to improve the skewed distribution. To analyze the HOMA-IR values as categorical variables, the levels were divided into sex-specific quartiles: HOMA-IR: Q1, less than or equal to 0.88; Q2, 0.89 to 1.31; Q3, 1.32 to 2.02; and Q4, greater than or equal to 2.03 for men; Q1, less than or equal to 0.89; Q2, 0.90 to 1.29; Q3, 1.30 to 1.93; and Q4, greater than or equal to 1.94 for women. Regression analysis was used to assess trends for the mean values of risk factors across the HOMA-IR levels, and logistic regression analysis for the frequencies. The linear trends in IOP values across the HOMA-IR levels were tested using a linear regression model. In the multivariable-adjusted analysis, we included the following possible risk factors for increased IOP: age, sex, systolic blood pressure, diabetes, total cholesterol, HDL cholesterol, BMI, waist circumference, smoking habits, alcohol intake, and regular exercise.[6,10] Age, systolic blood pressure, BMI, waist circumference, total cholesterol, and HDL cholesterol were treated as continuous variables, and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor; *P* less than 0.05 was considered statistically significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University institutional review board for clinical research, and

Table 2. Age- and Sex-Adjusted and Multivariable-Adjusted Mean Values of IOP According to the Quartiles of HOMA-IR Levels and Increase in IOP per Every 1-Log-Transformed HOMA-IR, The Hisayama Study, 2007

		Age- and Sex-Adjusted			Multivariable-Adjusted*		
Categorical Variable	*n*	IOP, mm Hg	*P* for Trend	*P*	IOP, mm Hg	*P* for Trend	*P*
HOMA-IR levels†							
Quartile 1	563	13.3 (0.1)			13.5 (0.1)		
Quartile 2	564	13.6 (0.1)			13.7 (0.1)		
Quartile 3	564	13.6 (0.1)			13.6 (0.1)		
Quartile 4	563	14.2 (0.1)	<0.0001		14.0 (0.1)	0.003	
Continuous variable							
Per every 1-log-transformed HOMA-IR	2254	0.52 (0.1)		<0.0001	0.32 (0.1)		0.003

Values are least-square means and (SE).

* Multivariable adjustment was made for age, sex, systolic blood pressure, diabetes, total cholesterol, HDL cholesterol, BMI, waist circumference, smoking habits, alcohol intake, and regular exercise.

† The HOMA-IR levels were divided into sex-specific quartiles: men, Q1, ≤0.88; Q2, 0.89 to 1.31; Q3, 1.32 to 2.02; and Q4, ≥2.03; women, Q1, ≤0.89; Q2, 0.90 to 1.29; Q3, 1.30 to 1.93; and Q4, ≥1.94.

it was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Results

Table 1 shows the mean values or frequencies of possible relevant factors of IOP by HOMA-IR quartile levels. The mean values of fasting serum glucose, fasting plasma insulin, systolic and diastolic blood pressures, total cholesterol, BMI, and waist circumference, and frequencies of diabetes and hypertension increased significantly with elevated HOMA-IR levels (all $P < 0.05$). Subjects with higher HOMA-IR levels were likely to have lower mean values of HDL cholesterol and lower frequencies of current smoking and current drinking (all $P < 0.05$). The characteristics of the study population sorted by IOP quartiles are shown in Supplementary Table S1.

Table 3. Age- and Sex-Adjusted and Multivariable-Adjusted Increase in IOP per Every 1-Log-Transformed HOMA-IR in the Subgroups of Potential Risk Factors, The Hisayama Study, 2007

Variable	*n*	Age- and Sex-Adjusted Increase in IOP, mm Hg	*P*	*P* for Interaction	Multivariable-Adjusted Increase in IOP, mm Hg*	*P*	*P* for Interaction
Sex, men	1005	0.57 (0.1)	<0.0001	0.45	0.23 (0.2)	0.18	0.08
Sex, women	1249	0.45 (0.1)	<0.0001		0.34 (0.1)	0.01	
Age, 40–64, y	1431	0.50 (0.1)	<0.0001	0.59	0.42 (0.1)	0.002	0.44
Age, ≥65 y	823	0.59 (0.1)	<0.0001		0.34 (0.2)	0.05	
Diabetes (−)	2044	0.44 (0.1)	<0.0001	0.57	0.32 (0.1)	0.004	0.42
Diabetes (+)	210	0.55 (0.3)	0.03		0.27 (0.3)	0.41	
Hypertension (−)	1271	0.32 (0.1)	0.004	0.21	0.34 (0.1)	0.02	0.43
Hypertension (+)	983	0.49 (0.1)	<0.0001		0.40 (0.2)	0.01	
Hypercholesterolemia (−)	1383	0.56 (0.1)	<0.0001	0.35	0.29 (0.1)	0.03	0.35
Hypercholesterolemia (+)	871	0.40 (0.1)	0.003		0.32 (0.2)	0.06	
Reduced HDL cholesterol (−)	2096	0.52 (0.1)	<0.0001	0.91	0.24 (0.1)	0.02	0.75
Reduced HDL cholesterol (+)	158	0.49 (0.4)	0.19		0.08 (0.4)	0.85	
BMI, <25.0, kg/m^2	1684	0.32 (0.1)	0.002	0.09	0.20 (0.1)	0.08	0.23
BMI, ≥25.0, kg/m^2	570	0.70 (0.2)	0.0003		0.50 (0.2)	0.02	
BMI, <27.5, kg/m^2	2042	0.43 (0.1)	<0.0001	0.14	0.26 (0.1)	0.02	0.14
BMI, ≥27.5, kg/m^2	212	0.92 (0.3)	0.002		0.74 (0.3)	0.02	
Smoking habits (−)	1745	0.46 (0.1)	<0.0001	0.12	0.23 (0.1)	0.05	0.17
Smoking habits (+)	509	0.76 (0.2)	<0.0001		0.61 (0.2)	0.01	
Alcohol intake (−)	1098	0.64 (0.1)	<0.0001	0.41	0.43 (0.1)	0.003	0.63
Alcohol intake (+)	1155	0.48 (0.1)	<0.0001		0.21 (0.2)	0.17	
Regular exercise (−)	1976	0.56 (0.1)	<0.0001	0.24	0.37 (0.1)	0.001	0.10
Regular exercise (+)	270	0.23 (0.2)	0.34		−0.04 (0.3)	0.89	

Value indicates β estimate and (SE). HOMA-IR was transformed to logarithm.

* Multivariable adjustment was made for age, sex, systolic blood pressure, diabetes, cholesterol, HDL cholesterol, BMI, waist circumference, smoking habits, alcohol intake, and regular exercise.

The mean IOP for the entire study population was 13.7 ± 2.6 mm Hg (range, 7.0–26.0 mm Hg) in the right eye and 13.6 ± 2.6 mm Hg (range, 6.0–27.0 mm Hg) in the left eye. The age- and sex-adjusted mean values of IOP significantly increased with higher quartile levels of HOMA-IR ($P < 0.0001$; Table 2). There was a similar association when continuous values of HOMA-IR were used instead of quartile levels (increase in IOP per every 1-log-transformed HOMA-IR; $P < 0.0001$). These associations remained unchanged after adjustment for potential confounding factors (both $P = 0.003$). We also investigated the age- and sex-adjusted and multivariable-adjusted increase in IOP per every 1-log-transformed HOMA-IR in the subgroups of potential risk factors (Table 3). There was no evidence of significant interaction in the magnitude of the association between the subgroups (all P for interaction > 0.08; Table 3).

Discussion

This study demonstrated that increased HOMA-IR levels, a surrogate index of insulin resistance, was significantly associated with elevated IOP after adjusting for known risk factors in a general Japanese population. Furthermore, the subgroup analyses of confounding factors showed that these factors had no significant modifying effect on the association between HOMA-IR and IOP. These findings suggest that insulin resistance, taking confounding factors into consideration, has an important role in the regulation of IOP.

Three clinical studies in Korea have assessed the association of metabolic syndrome and insulin resistance with IOP.[7–9] Two studies reported that IOP was significantly elevated with increasing HOMA-IR levels, which is in concordance with the present study. Chun et al.[9] showed that IOP was positively associated with HOMA-IR levels in individuals with BMI of less than 27.5 kg/m^2, but not in those with BMI of 27.5 kg/m^2 or more. In contrast, we found that the association between HOMA-IR and IOP was significant in the participants with BMI above and below 27.5 kg/m^2. The reason for the discrepancy between these studies in the finding for obese individuals is unclear, although it may due to chance or variations in samples. Further investigations would be needed to clarify this issue.

The precise mechanisms by which insulin resistance influences IOP have not been clearly elucidated. However, some studies have suggested the possible mechanisms involved in this process. First, insulin resistance and compensatory hyperinsulinemia have been demonstrated to stimulate sympathetic nervous system activity.[21] Stimulation of cervical sympathetic nerves increases IOP,[22] and adrenergic receptor polymorphisms, which are known to be related to sympathetic nerves, play an important role in the regulation of IOP.[23,24] Thus, insulin resistance may increase IOP by the process of stimulation of the sympathetic nervous system. Second, as another possible mechanism other than neural factors, vascular endothelial dysfunction caused by insulin resistance and subsequent reduced production of nitric oxide (NO) may be involved in the elevation of IOP. Nitric oxide decreases IOP by increasing aqueous outflow facility in the trabecular meshwork.[25] Thus, impairment of NO production possibly contributes to the increased IOP. Last, IOP is determined by aqueous fluid production and outflow. Aquaporin (AQP) water channels are expressed in the eye at sites of aqueous fluid production and outflow.[26] Aquaporin is expressed in great abundance in adipose tissue,[27] and loss of AQP induces insulin resistance.[28] The expression or effect of AQP and adipocyte hypertrophy may have effect on insulin resistance and IOP. There could be other mechanism for explaining this. Further studies are necessary to clarify the hypothesis.

Our study begins to define the association between insulin resistance and elevation of IOP in a general Japanese population. It is significant because of the large sample size and high response rate (72.6%). Nevertheless, there are some limitations that should be taken into consideration. First, our findings were based on a single measurement of plasma glucose and insulin concentration that might not capture various ranges of HOMA-IR levels in fasting participants. Second, some misclassification of the insulin resistance levels might have occurred because the HOMA-IR is a surrogate index for insulin resistance. Considering the influence of these limitations, our study could have underestimated the role of insulin resistance in the elevation of IOP. Thus, based on our current data, the association could be even stronger than is apparent. Last, because this is a cross-sectional study, interpretation of the causal relationship between HOMA-IR and IOP is limited. However, we believe that insulin resistance affects IOP levels because IOP itself is unlikely to induce systemic insulin resistance.

In conclusion, increasing insulin resistance, as evaluated by HOMA-IR, is a significant independent risk factor for the elevation of IOP in the general populations. In the subgroup analyses, there is no evidence of significant interaction in the association between HOMA-IR and IOP. Thus, insulin resistance per se may be a strong risk factor for elevation of IOP.

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