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網膜静脈閉塞症と慢性腎臓病の関連.
第63回日本臨床眼科学会、2009年10月　福岡市

G．知的所有権の取得状況

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High Serum Bilirubin Levels and Diabetic Retinopathy

The Hisayama Study

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Purpose: To assess the association between serum total bilirubin levels and diabetic retinopathy prevalence in participants of the Hisayama Study who had diabetes and impaired glucose metabolism.

Design: Population-based, cross-sectional study.

Participants: Of 3119 participants of the Hisayama Study Eye Examinations in 2007, Japan, 1672 aged ≥40 years with either diabetes or impaired glucose metabolism (defined by a 75-g oral glucose tolerance test) were enrolled in the present study.

Methods: Diabetic retinopathy was assessed via ophthalmic examination after pupil dilatation. The presence and the severity of diabetic retinopathy were determined by grading of color fundus photographs using the modified Airlie House classification system. Association of diabetic retinopathy with serum bilirubin quartiles was assessed using logistic regression model adjusting for age and known risk factors for diabetic retinopathy.

Main Outcome Measures: Prevalent diabetic retinopathy.

Results: Diabetic retinopathy was present in 70 of 1672 (4.2%) participants. The prevalence of diabetic retinopathy in persons with the highest bilirubin quartile (≥0.9 mg/dL) was 2.7%, compared with the prevalence of 3.4%, 5.1%, and 5.1% in those with the first (<0.6 mg/dL), second (0.6–0.69 mg/dL), and third quartiles (0.7–0.89 mg/dL). After adjusting for factors known to be associated with diabetic retinopathy, the prevalence was significantly lower among persons with the highest bilirubin quartile compared with those with the lowest quartile (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.09–0.72) or compared with those in the 3 lower quartiles (OR, 0.25; 95% CI, 0.11–0.58).

Conclusions: Elevated serum bilirubin levels may be protective against diabetic retinopathy among persons with either diabetes or impaired glucose metabolism, independent of known risk factors for diabetic retinopathy.

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Diabetic retinopathy (DR) is a common complication of diabetes and is among the leading causes of blindness and visual impairment among working age persons in developed countries.[1] A number of population-based studies have reported retinopathy lesions not only present in persons with diabetes but also in persons with impaired glucose tolerance or impaired fasting glucose.[2]

Bilirubin has been recognized as an important endogenous antioxidant.[3] In several prospective studies, an inverse relationship has been reported between high bilirubin levels and cardiovascular disease[4] as well as coronary heart disease.[5–7] Cross-sectional studies reported similar protective associations of bilirubin levels with coronary artery disease,[8] peripheral vascular disease,[9] carotid intimal medial thickness,[10] and stroke.[11] This inverse relationship of bilirubin levels to cardiovascular disease was confirmed by a meta-analysis,[12] and bilirubin has now been discussed as a therapeutic target for cardiovascular disease.[13] However, several clinical studies have examined the associations between serum bilirubin levels and retinopathy of prematurity and concluded that there is no protective effect of bilirubin on the development of this retinopathy.[14,15]

Although bilirubin has been recognized as an endogenous inhibitor of cardiovascular disease,[4–12] the relationship between bilirubin and diabetic vascular complications has not been fully understood, with limited relevant reports available.[16–18] There has been no population-based study about the association between serum bilirubin levels and DR. We therefore aimed to examine the association between serum bilirubin levels and DR in patients with diabetes and impaired glucose metabolism in a general Japanese population.

Materials and 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 adjoining Fukuoka City, a metropolitan area in southern Ja-

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pan.[19,20] As a part of the study, an epidemiologic study of eye disease among residents of the town has been underway since 1998.[20] In 2007, of the 4298 residents aged ≥40 years, 3119 (79.8%) consented to participate and underwent an ophthalmic examination for the present study; of these, 2880 (92.3%) underwent a 75-g oral glucose tolerance test. Of the 2880 subjects examined, 1672 (58.1%; 466 with diabetes, 583 with impaired glucose tolerance, and 623 with impaired fasting glucose) were included in this study.

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Ophthalmic Examination and Definition of Diabetic Retinopathy

The methods used for the ophthalmic examination have been described in detail previously.[21] Briefly, each participant underwent comprehensive ophthalmic examination, including stereoscopic fundus examination using indirect ophthalmoscopy, and examination with a slit lamp biomicroscope with a "superfield lens" (Volk, Mentor, OH) after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken from both eyes of each participant using a Topcon digital TRC NW-6SF fundus camera (Topcon Corporation, Tokyo, Japan). The photographs were taken in 1-field per eye, centered on the macula. The presence of DR was determined based on both fundus examinations using indirect ophthalmoscopy and slit lamp, and grading of color fundus photographs. The photographs were assessed by photographic graders who were masked to clinical information, following the modified Airlie House Diabetic Retinopathy Classification System, and classified as (i) no retinopathy, (ii) mild retinopathy, (iii) moderate retinopathy, or (iv) proliferative retinopathy.[22,23] The presence of any DR was defined as the presence of mild or moderate or proliferative retinopathy in either eye.

Data Collection

Blood samples were collected from an antecubital vein after an overnight fast for the determination of the serum bilirubin, lipid, gamma-glutamyl transpeptidase, plasma glucose, and hemoglobin A_{1c} levels. After the fasting blood specimen had been taken, the 75-g oral glucose tolerance test was performed between 08.00 and 10.30 hours. 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. The serum bilirubin concentration was measured enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan). The normal range of serum total bilirubin levels as measured used in the study was 0.3 to 1.2 mg/dL. The plasma glucose concentration was determined using the glucose-oxidase method, and the hemoglobin A_{1c} levels were measured by the high-pressure lipid chromatographic assay. Serum total cholesterol and high-density lipoprotein cholesterol were determined enzymatically using the same autoanalyzer, and gamma-glutamyl transpeptidase was measured using Orlowsky's method.

Diabetes classification was based on plasma glucose results, using the 2003 American Diabetes Association criteria.[24] Diabetes was diagnosed on the basis of fasting plasma glucose (FPG) of ≥126 mg/dL (7.0 mmol/L), 2-hour postload plasma glucose (2-hour PG) of ≥ 200 mg/dL (11.1 mmol/L), or current treatment with insulin or oral hypoglycemic medication, impaired glucose tolerance was defined if FPG <126 mg/dL (7.0 mmol/L) and 2-hour PG ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L), and impaired fasting glucose was defined if FPG ≥100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L) and 2-hour PG <140 mg/dL (7.8 mmol/L). Blood pressure was measured 3 times after the subject had rested for ≥5 minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Body height and weight were measured in light clothing without shoes, and the body mass index was calculated as the weight in kilograms divided by the height in meters squared. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire, and 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 ≥3 times per week during their leisure time were designated the regular exercise group. The questionnaire also covered questions about histories of cardiovascular disease, including stroke and coronary heart disease.

Statistical Methods

Age-adjusted prevalence of DR was calculated via direct standardization to the whole Hisayama Study population. A linear pattern of the association was assessed initially for per unit change in bilirubin levels associated with DR prevalence. We further divided bilirubin levels into quartiles (<0.60, 0.60–0.69, 0.70–0.89, and ≥0.90 mg/dL), and considered the lowest quartile or the 3 lower quartiles as reference. Test for trend across quartiles was performed in the logistic regression model. The age- and gender-adjusted or multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In the multivariable-adjusted analysis, we included possible associated factors of either DR or serum bilirubin level that were available in our study, namely, age, gender, 2-hour PG, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, smoking habits, alcohol intake, and history of cardiovascular disease. We also performed additional analysis restricted to subjects with diabetes. In the multivariable-adjusted analysis of this subsample, we included risk factors for DR, namely, age, gender, duration of diabetes, hemoglobin A_1c, insulin treatment, and history of cardiovascular disease. The SAS software package (SAS Inc., Cary, NC) was used to perform all statistical analyses. A 2-sided $P<0.05$ was considered significant.

Results

Of the study participants, 70 (4.2%) were found to have DR. Mild, nonproliferative retinopathy (category ii), moderate retinopathy (category iii), and proliferative retinopathy (category iv) were found in 40 (2.4%), 29 (1.7%), and 1 (0.1%) participants, respectively.

Participants with DR were more likely to be men (Table 1). The mean age and mean levels of FPG, 2-hour PG, hemoglobin A_{1c} and systolic blood pressure, the frequency of hypertension and having history of cardiovascular disease were significantly higher among subjects with DR, whereas the mean level of total cholesterol and the frequency of smoking habits were significantly lower in those with DR (Table 1). Furthermore, we compared the mean values or frequencies of risk factors between subjects having diabetes with DR and those without DR. The mean duration of diabetes and mean hemoglobin A_{1c}, and the frequency of insulin treatment and history of cardiovascular disease were significantly higher among subjects with DR (Table 1).

Table 1. Characteristics of Subjects by Status of Diabetic Retinopathy

Variable	Without Diabetic Retinopathy	With Diabetic Retinopathy
All subjects (n)	1602	70
Age (y)	64±11	68±10**
Men (%)	52.5	72.9**
Bilirubin level (mg/dL)	0.78±0.32	0.76±0.30
Fasting plasma glucose (mmol/L)	6.1±1.2	8.7±2.5**
2-hour post-load plasma glucose (mmol/L)	9.1±3.9	18.0±5.1**
Hemoglobin A_1c (%)	5.3±0.8	7.0±1.4**
Systolic blood pressure (mmHg)	135±18	142±17**
Diastolic blood pressure (mmHg)	82±10	81±11
Hypertension (%)	57.7	77.1**
Total cholesterol (mmol/L)	5.5±0.9	5.1±0.8**
High-density lipoprotein cholesterol (mmol/L)	1.7±0.4	1.7±0.4
Gamma-glutamyl transpeptidase (IU/L)	3.5±0.8	3.7±0.9
Body mass index (kg/m^2)	23.9±3.5	24.5±3.6
History of cardiovascular disease (%)	4.9	22.9**
Smoking habits (%)	21.3	11.4*
Alcohol intake (%)	51.9	51.4
Regular exercise (%)	12.7	10.0
Subjects with diabetes (n)	398	68
Duration of diabetes (year)	5.7±4.9	16.2±8.8**
Hemoglobin A_1c (%)	6.1±1.1	7.0±1.4**
Insulin treatment (%)	1.3	17.7**
History of cardiovascular disease (%)	9.5	23.5**
Duration of diabetes (y)	5.7±4.9	16.2±8.8**

Values are expressed as means ± standard deviation or percentages. Serum gamma-glutamyl transpeptidase was transformed to logarithm.
*$P<0.05$, **$P<0.01$ versus without diabetic retinopathy.

Table 2 compares the mean values or frequencies of potential factors associated with DR by bilirubin quartiles. Subjects with higher bilirubin levels were more likely to be men. Among subjects with the highest quartile of bilirubin levels, the mean values of 2-hour PG and high-density lipoprotein cholesterol were significantly higher, although the mean values of total cholesterol, the frequencies of history of cardiovascular disease or smoking were significantly lower, compared with subjects in other 3 lower quartiles. The prevalence of DR in persons with the highest bilirubin quartile (≥0.9 mg/dL) was 2.7%, compared with the prevalence of 3.4%, 5.1% and 5.1%, respectively, in those within the first (<0.6 mg/dL), second (0.6–0.69 mg/dL), and third (0.7–0.89 mg/dL) quartiles (Table 2).

When bilirubin levels were assessed continuously, we found that each 0.1 mg/dL increase in bilirubin levels was associated with a 16% reduction of the likelihood of having DR (OR, 0.84; 95% CI, 0.76–0.93), after multivariable adjustment. Compared with persons in the lowest quartile of bilirubin levels, those with the highest quartile had a significantly lower odds of having DR, after adjustment for age, gender, 2-hour PG, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, history of cardiovascular disease, smoking habits, and alcohol intake (OR, 0.25; 95% CI, 0.09–0.72; Table 3). When the lower 3 quartiles were combined to form a reference group, persons in the highest quartile also had reduced prevalence of DR (OR, 0.25; 95% CI, 0.11–0.56). We also examined the age- and gender-adjusted OR of having DR by quartiles of serum total bilirubin levels among subjects with diabetes. The OR of DR decreased as quartiles of bilirubin levels increased, but the trend did not reach significance ($P = .07$), probably because of the small number of subjects. This association did not change even after adjustment for age, gender, duration of diabetes, hemoglobin A_1c level, insulin treatment, and history of cardiovascular disease (Table 3).

Discussion

We investigated the association of serum bilirubin levels with DR among participants of Hisayama Study who had either diabetes or impaired glucose metabolism. After adjusting for age, gender, and known risk factors for DR, serum bilirubin level was found to be independently and inversely associated with the prevalence of DR. Persons with diabetes or impaired glucose metabolism who were also in the highest quartile of bilirubin levels were 75% less likely to have DR, compared with those in the lowest quartile. Although this observed protective association of bilirubin with DR is in keeping with the documented protective associations of bilirubin with cardiovascular disease and the antioxidant property of bilirubin,[4–12] our findings need to be confirmed in future studies.

Several clinical studies have examined the association between serum bilirubin and diabetic vascular complications.[16–18] Among these, 2 case-control studies reported the association between serum bilirubin level and DR, and the findings were inconsistent.[16,17] One study showed that although serum bilirubin concentrations were significantly higher among normal subjects compared with patients with diabetes, there was no significant difference in mean serum bilirubin levels between patients having diabetes with DR and those without DR.[16] The other study reported a lower prevalence of diabetic vascular complications (retinopathy, macroalbuminuria, coronary artery disease, and cerebrovascular disease) in patients with both diabetes and Gilbert's syndrome, a congenital hyperbilirubinemia defined as serum bilirubin level >1.2 mg/dL.[17] Our findings are consistent with those of the latter report.

Mechanisms underlying the protective association of bilirubin with DR are not yet fully understood, and possible explanations have been proposed. Bilirubin has been recognized as an endogenous antioxidant[1] and suppresses inflammation in the vasculature.[5] The microvasculature of the retina responds to hyperglycemic milieu through a number of biochemical changes, including increased oxidative stress, polyol pathway, protein kinase C activation, and advanced glycation end product formation.[25] Oxidative stress and inflammation are considered crucial contributors in the pathogenesis of DR.[25,26] Oxidative stress-induced biochemical changes contribute to both functional and structural changes in the retina microvasculature, including basement membrane thickening, microvascular cell loss, capillary closure, and acellular capillary formation.[27] Structural changes may contribute to, and also result from, functional changes such as altered blood flow, loss of intercellular junctions, and increased vessel permeability. Animal models of DR have shown beneficial effects of antioxidants on the development of retinopathy in diabetic rats.[25] An-

Table 2. Mean Values or Frequencies of Relevant Factors by Quartiles of Serum Total Bilirubin Levels

Variable	Quartile of Serum Total Bilirubin Level (mg/dL)				P-Value for Trend
	<0.6	0.6–0.69	0.7–0.89	≥0.9	
n	358	548	396	370	
Age (y)	63±11	64±11	64±10	64±11	0.22
Men (%)	54.2	47.8	51.5	62.7	<0.001
Diabetic retinopathy (%)	3.4	5.1	5.1	2.7	0.65
Fasting plasma glucose (mmol/L)	6.2±1.4	6.2±1.3	6.3±1.5	6.2±1.3	0.45
2-hour post-load plasma glucose (mmol/L)	8.6±3.8	9.6±4.4	9.8±4.7	9.9±4.4	<0.001
Hemoglobin A_1c (%)	5.4±0.8	5.4±0.8	5.5±1.0	5.3±0.9	0.09
Systolic blood pressure (mmHg)	135±17	135±18	136±19	137±18	0.34
Diastolic blood pressure (mmHg)	81±10	81±10	82±10	83±10	0.06
Hypertension (%)	55.6	57.1	61.9	59.7	0.29
Total cholesterol (mmol/L)	5.4±0.9	5.5±0.9	5.5±0.9	5.3±0.9	0.005
High-density lipoprotein cholesterol (mmol/L)	1.5±0.4	1.7±0.4	1.7±0.4	1.7±0.5	<0.001
Gamma-glutamyl transpeptidase (IU/L)	3.5±0.8	3.5±0.7	3.5±0.8	3.6±0.8	0.51
Body mass index (kg/m^2)	24.1±3.4	23.9±3.2	24.1±3.8	23.7±3.5	0.43
History of cardiovascular disease (%)	9.2	5.1	4.5	4.5	0.002
Smoking habits (%)	33.5	20.6	17.7	12.4	<0.001
Alcohol intake (%)	51.7	49.3	50.0	58.1	0.05
Regular exercise (%)	12.3	12.1	10.7	15.7	0.19

Values are expressed as the means ± standard deviation or percentages. Serum gamma-glutamyl transpeptidase was transformed to logarithm.

other experimental study of animals has shown that inhibition of the inflammatory cascade at any stage of disease course could inhibit the progression of early stage DR.[25] Therefore, it is possible that an increase in serum bilirubin level inhibits oxidative stress and inflammation processes and thus slows or interrupts the pathways to the development of DR.

Before adjustment for other known DR risk factors, subjects with the highest quartile of bilirubin levels had a significantly higher mean value of 2-hour PG levels than subjects in other quartiles. The findings were carefully rendered to ensure that there was no mistake in the findings presented in this report. Our data seem to indicate a countereffect of elevated bilirubin levels against the effect of elevated 2-hour PG levels on DR prevalence. We also documented that the protective effect of elevated bilirubin level on DR prevalence was independent of other DR risk factors, suggesting that the underlying mechanisms for the

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Diabetic Retinopathy by Quartiles of Serum Total Bilirubin Levels*

	Quartile of Serum Total Bilirubin Level (mg/dL)				P Value for Trend
	<0.6	0.6–0.69	0.7–0.89	≥0.9	
All subjects					
Population at risk (n)	358	548	396	370	0.35
Case of diabetic retinopathy (n)	12	28	20	10	
Age- and gender-adjusted OR (95% CI)	1.0	1.59 (0.79–3.18)	1.55 (0.74–3.23)	0.70 (0.30–1.66)	
Multivariable-adjusted OR (95% CI)	1.0	1.11 (0.48–2.57)	0.86 (0.35–2.11)	0.25 (0.09–0.72)*	0.004
Subjects with diabetes					
Population at risk (n)	83	151	116	116	0.09
Case of diabetic retinopathy (n)	11	28	19	10	
Age- and gender-adjusted OR (95% CI)	1.0	1.41 (0.65–3.03)	1.27 (0.56–2.87)	0.52 (0.21–1.31)	
Multivariable-adjusted OR (95% CI)	1.0	1.41 (0.56–3.54)	1.12 (0.41–3.01)	0.39 (0.12–1.30)	0.07

Multivariable adjustment was made for age, gender, 2-hour post-load plasma glucose, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, gamma-glutamyl transpeptidase, history of cardiovascular disease, smoking habits, and alcohol intake.
*$P<0.01$versus first quartile.

association with bilirubin levels are likely different from the common pathway via elevated serum blood glucose levels. If confirmed, this may provide a new therapeutic approach to complement current available therapies for patients with diabetes (e.g., lowering serum glucose, lipid levels, and blood pressure levels).

In our data, there also seemed to be a threshold of bilirubin levels at the highest quartile (≥0.9 mg/dL) for the significant protective effect on DR (Table 2). However, because of the relatively small numbers of DR cases in this group, caution should be taken and confirmation of our findings in studies with large sample size is necessary.

Several limitations of our study should be discussed. Our findings were based on a single serum bilirubin level measurement, which might not capture various ranges of bilirubin levels over times in particular participants. However, if such a variation is random and nondifferentiated between cases and controls, it would only dilute the association and bias the results toward the null. A cross-sectional association has no implication of causal relationship. Because the numbers of DR cases were relatively small in our sample, particularly in the highest quartile of bilirubin group, we cannot exclude the possibility of a chance finding.

In conclusion, we demonstrated that elevated serum bilirubin levels were significantly associated with low prevalence of DR in persons with diabetes or impaired glucose metabolism, independent of known DR risk factors. Further studies with a larger sample size, either cross-sectional or prospective, are needed to confirm these findings. If confirmed, our finding may have important implications to clinical management of diabetes and to the prevention of diabetic complications.

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Nine-Year Incidence and Risk Factors for Retinal Vein Occlusion in a General Japanese Population: The Hisayama Study

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Purpose. To estimate the long-term cumulative incidence and risk factors for retinal vein occlusion (RVO) in a population-based cohort study of Japanese.

Methods. In 1998, a total of 1775 individuals aged 40 years or older underwent a baseline eye examination. Of those, 1369 subjects (77.1%) took part in the follow-up eye examination in 2007 and were enrolled in the present study. Each participant underwent a comprehensive examination. The diagnosis of RVO, including branch (BRVO) and central RVO (CRVO), was determined by grading color fundus photographs. Logistic regression analysis was performed to determine risk factors for RVO.

Results. The 9-year cumulative incidence of RVO was 3.0% (2.7% for BRVO and 0.3% for CRVO). The age-specific cumulative incidence of RVO significantly increased with age (P for trend = 0.03). After adjusting for age and sex, higher diastolic blood pressure and chronic kidney disease (CKD) were significantly associated with RVO. In multivariate analysis, higher diastolic blood pressure (per 10 mm Hg) (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.14 to 2.01) and CKD (OR, 2.23; 95% CI, 1.02 to 4.89) remained independently significant risk factors for RVO. In stratified analysis, the risk of RVO was higher in subjects with CKD than that in subjects without CKD in both the nonhypertension and the hypertension groups.

Conclusions. These findings suggest that the incidence of RVO is higher in Japanese than that in other Asians and Caucasians, and that higher blood pressure and CKD are independent risk factors for RVO in the Japanese. (*Invest Ophthalmol Vis Sci.* 2011;52:5905-5909) DOI:10.1167/iovs.11-7775

Retinal vein occlusion (RVO) is one of the causes for significant loss of vision in elderly populations in developed countries.[1] Despite the magnitude of this problem, the available treatment options remain limited.[2,3] Furthermore, RVO has also been associated with increased risk of cardiovascular disease.[4-6] It is thus very important to determine the prevalence of RVO and to identify its systemic risk factors to develop preventive measures for the disease. To date, several population-based studies,[6-11] mostly in Caucasian populations, have provided valuable information on the incidence and risk factors for RVO. The risk factors reported include hypertension,[6-11] diabetes,[10] smoking habits,[10] dyslipidemia,[7,9] and a history of angina.[9] However, there have been only a limited number of population-based epidemiologic studies on RVO in Japanese and in other Asians,[9,11,12] and information on the long-term risk of RVO is nonexistent in Asians including Japanese.

The purpose of this article was to examine the 9-year incidence of RVO and its risk factors in a prospective study of a general Japanese population.

Materials and 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 adjoining Fukuoka City, a metropolitan area in southern Japan.[13,14] As a part of the study, a follow-up survey of eye diseases among residents of the town has been under way.[15] In 1998, a total of 1775 individuals (688 males, 1087 females) aged 40 years or older underwent a baseline eye examination. Of those, 1404 subjects (79.1%) took part in the follow-up eye examination in 2007. After excluding 35 subjects with RVO at the baseline examination, the remaining 1369 subjects (508 males, 861 females, 77.1% of the original cohort) were enrolled in the present study.

Assessment of RVO

The methods used for the baseline eye examination have been described in detail previously.[15] Briefly, each participant underwent comprehensive ophthalmic examination, including stereoscopic fundus examination using indirect ophthalmoscopy, and examination with a slit-lamp biomicroscope with a "superfield lens" (Volk Optical Inc., Mentor, OH) after pupil dilatation with 1.0% tropicamide and 5% phenylephrine. Fundus photographs (45°) were taken using a fundus camera (Topcon TRC NW-5; Topcon Corporation, Tokyo, Japan), and the 35-mm color transparencies were made using color slide film (Fujichrome, Sensia II; Fujifilm, Tokyo, Japan). In the 9-year follow-up eye examination, fundus photographs (45°) were taken using digital fundus camera (Topcon TRC NW-6SF; Topcon). In both examinations, we took one photographic field centered on a point midway between the temporal edge of the optic disc and the fovea in both eyes and used a similar masked photographic grading technique. The presence of RVO was determined based on the grading of fundus examinations by indirect ophthalmoscopy, slit-lamp, and color fundus photographs. All photographs were evaluated by retinal specialists (MY and TI) who were masked to participant data. The presence or absence of either central or branch RVO (CRVO or BRVO, respectively) was defined according to a standardized protocol.[10,16] Recent CRVO was characterized by widespread scattered superficial or deep retinal hemor-

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rhages with or without optic disc hyperemia or edema, venous dilatation, retinal edema, or occluded or sheathed veins. Old CRVO was diagnosed by the presence of anastomotic vessels on the disc. For hemispheric RVO, these signs were present in the upper or lower retinal half, corresponding to the branch of the central vein in which the occlusion occurred. BRVO was characterized by retinal hemorrhages occurring within the retinal sector corresponding to the blood supply sector of the occluded venule and by scattered superficial and deep retinal hemorrhages, venous dilatation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. Old BRVO was characterized by the presence of collateral vessels or intraretinal microvascular abnormalities in a retinal sector. The presence of any RVO was defined as the presence of BRVO or CRVO in either eye.

Assessment of Other Variables

Blood pressure was measured three times from subjects in a sitting position after each subject had rested for at least 5 minutes, and the average of the three measurements was used for the analysis. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medication. Body height and weight were measured from subjects in light clothing without shoes, and the body mass index (kg/m^2) was calculated.

Serum total cholesterol levels were measured enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan). Plasma glucose concentrations were determined by the glucose-oxidase method, and diabetes was defined by a 75-g oral glucose tolerance test, by fasting (≥7.0 mM) or postprandial (≥11.1 mM) blood glucose levels or by the use of hypoglycemic agents. Hematocrit levels were determined using an automated blood cell counter (Coulter STKS; Coulter Inc., Hialeah, FL).

At the baseline examination, fresh voided urine samples were tested by the dipstick method, and proteinuria was defined as ≥1+. Serum creatinine was measured by the Jaffe method using an autoanalyzer (TBA-80S; Toshiba). The Jaffe method value was converted to an enzymatic method value using the following equation[17]:

$$\text{Serum creatinine (enzymatic method [mg/dL])} = \text{Serum creatinine (Jaffe method [mg/dL])} - 0.207.$$

The estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry-traceable creatinine-based four-variable modification of diet in renal disease (IDMS-MDRD) study equation.[18] eGFR was derived using the following equation modified for Japanese:

$$\text{eGFR (mL/min/1.73 m}^2) = 175 \times \text{serum creatinine}^{-1.154} \times \text{age (years)}^{-0.203} \times 0.808 \times 0.742 \text{ (if female)}.$$

We defined CKD as the presence of proteinuria and/or eGFR <60 mL/min/1.73 m^2.[19] Information on smoking habits and alcohol intake was obtained using a standard questionnaire administered by trained interviewers at the initial examination. Subjects were classified either as current habitual users or as nonusers.

Statistical Analysis

We calculated the 9-year incidences of RVO. Incident RVO was defined by the appearance at follow-up of either BRVO or CRVO in either eye of persons in whom no BRVO or CRVO was present at baseline. We examined the relationships between risk factors at baseline and the incidence of RVO. We considered the following 13 possible risk factors for RVO: age, sex, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, body mass index, chronic kidney disease (CKD), eGFR, smoking habits, alcohol intake, and hematocrit. Age, systolic blood pressure, diastolic blood pressure, total cholesterol, body mass index, and hematocrit 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, respectively. Mean values were compared by the Student's t-test and frequencies by χ^2 test. We estimated the age-adjusted and multivariate odds ratios (ORs) and their 95% confidence intervals (CIs) of each potential risk factor by using a logistic regression analysis. Heterogeneity in the relationship between subgroups of hypertension status was tested by adding a multiplicative interaction term to the relevant logistic model. A statistical software package (SAS version 9.2; SAS Institute, Cary, NC) was used to perform all statistical analyses. A two-sided value of $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by the Kyushu University Institutional Review Board for Clinical Research, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Table 1 shows the comparison of baseline characteristics between subjects with and without RVO. Subjects with RVO were older than those without RVO, but the proportion of males was not different. The mean values of systolic and diastolic blood pressures and the frequencies of hypertension and CKD were higher in subjects with RVO than values in subjects without RVO.

The age-specific 9-year cumulative incidence of RVO is shown in Table 2. Of the 1369 subjects at risk, 41 (3.0%) developed RVO during the follow-up. The cumulative incidence of BRVO was 2.7%, and that of CRVO was 0.3%. The age-specific cumulative incidence of RVO significantly increased with advancing age in all subjects (P for trend = 0.03). This trend was observed for females (P = 0.01), but not for males (P = 0.75).

Table 3 presents the results of age- and sex-adjusted and multivariate-adjusted logistic regression analyses of risk factors for the development of RVO. After adjusting for age and sex, higher diastolic blood pressure (per 10 mm Hg) (OR, 1.55; 95% CI, 1.16 to 2.05) and CKD (OR, 2.39; 95% CI, 1.10 to 5.20) were significant risk factors for the development of RVO. In multivariate analysis, diastolic blood pressure (OR, 1.51; 95%

Table 1. Characteristics of Study Population with or without Development of RVO: The Hisayama Study, 1998

Variable	Non-RVO (n = 1328)	RVO (n = 41)
Age, y	60.0 ± 10.0	63.0 ± 8.0*
Sex, Male %	37.0	39.0
Hypertension, %	40.7	56.1*
Systolic blood pressure, mm Hg	132.0 ± 21.0	140.0 ± 24.0*
Diastolic blood pressure, mm Hg	78.0 ± 10.0	82.0 ± 12.0**
Diabetes, %	10.7	14.6
Total cholesterol, mM	5.4 ± 0.9	5.3 ± 0.7
Body mass index, kg/m^2	23.2 ± 3.2	23.6 ± 3.2
Chronic kidney disease, %	10.2	24.4**
Estimated glomerular filtration rate, mL/min/1.73 m^2	77.7 ± 14.9	75.3 ± 17.2
Hematocrit, %	40.2 ± 3.9	40.6 ± 3.8
Smoking habits, %	16.1	22.0
Alcohol intake, %	37.9	31.7

Values are expressed as means ± SD or percentages. *$P < 0.05$, **$P < 0.01$, vs. non-RVO.

TABLE 2. Age-Specific 9-Year Cumulative Incidence of RVO by Sex: The Hisayama Study, 1998-2007

Group/ Age (y)	Population at Risk	Number of Cases (%)			*P* for Trend
		Branch RVO	Central RVO	All RVO	
Males					
40-49	73	2 (2.7)	0 (0.0)	2 (2.7)	
50-59	136	4 (2.9)	0 (0.0)	4 (2.9)	
60-69	183	4 (2.2)	2 (1.1)	6 (3.3)	
70+	116	4 (3.5)	0 (0.0)	4 (3.5)	0.75
Females					
40-49	177	1 (0.6)	0 (0.0)	1 (0.6)	
50-59	253	6 (2.4)	0 (0.0)	6 (2.4)	
60-69	272	10 (3.7)	1 (0.4)	11 (4.0)	
70+	159	6 (3.8)	1 (0.4)	7 (4.4)	0.01
All					
40-49	250	3 (1.2)	0 (0.0)	3 (1.2)	
50-59	389	10 (2.6)	0 (0.0)	10 (2.6)	
60-69	455	14 (3.1)	3 (0.7)	17 (3.7)	
70+	275	10 (3.6)	1 (0.4)	11 (4.0)	0.03
Total	1369	37 (2.70)	4 (0.29)	41 (2.99)	

CI, 1.14 to 2.01) and CKD (OR, 2.23; 95% CI, 1.02 to 4.89) remained independently significant risk factors for RVO.

Table 4 shows the age- and sex-adjusted ORs of elevated diastolic blood pressure and CKD for the development of RVO by hypertension status. In the hypertensive group, higher diastolic blood pressure and CKD significantly increased the risk of RVO, whereas no such associations were observed in the nonhypertensive group, probably due to the small number of RVO cases. The heterogeneity of the two groups was not significant for elevated diastolic blood pressure (*P* for heterogeneity = 0.69) and CKD (0.99).

DISCUSSION

The present study showed a 9-year cumulative incidence of RVO was 3.0% and found that higher diastolic blood pressure and CKD were independent risk factors for the development of RVO in a Japanese population. To our knowledge, this is the first population-based cohort study that investigated the long-term incidence and risk factors for RVO in Japan.

A few cohort studies have reported the cumulative incidence of RVO. In the Beaver Dam Eye Study (University of Wisconsin-Madison), the 15-year cumulative incidences of BRVO and CRVO were 1.8% and 0.5%, respectively.[16] Similar findings were obtained from the 10-year follow-up of the Blue Mountains Eye Study in Australia (BRVO, 1.2% and CRVO, 0.4%).[8] In Japan, one cohort study reported a 10-year RVO incidence of 0.4%.[20] Therefore, it has been believed that the incidence of RVO was much lower in Japanese than that in Caucasians. In that Japanese study, however, the study population was very small (n = 245), and the follow-up rate was very low (19.6%). In our large-scale population-based cohort, the 9-year incidence of RVO was 3.0% (BRVO, 2.7% and CRVO, 0.3%). This finding suggests that the incidence of RVO in Japanese is twofold higher than that in Caucasians. The reasons for this divergence are uncertain, but the differences in environmental and genetic factors among populations or perhaps the differences in methodology among studies may contribute to the variation of incidence. We diagnosed old CRVO using the findings of anastomotic vessels on the disc, which may be found in other diseases, such as optic nerve sheath meningioma, chronic glaucoma, and others. This may explain the higher incidence of RVO in our study.

TABLE 3. Age- and Sex-Adjusted and Multivariate-Adjusted Odds Ratio of Risk Factors for RVO: The Hisayama Study, 1998-2007

Variable	Odds Ratio (95% Confidence Interval)			
	Age- and Sex-Adjusted	*P*	Multivariate Model	*P*
Age, per 1 year			1.03 (0.99-1.06)	0.14
Sex, Males			1.19 (0.62-2.30)	0.60
Hypertension	1.61 (0.83-3.11)	0.16		
Systolic blood pressure, per 10 mm Hg	1.15 (0.99-1.32)	0.06		
Diastolic blood pressure, per 10 mm Hg	1.55 (1.16-2.05)	0.003	1.51 (1.14-2.01)	0.004
Diabetes	1.28 (0.52-3.12)	0.59		
Total cholesterol, per 1 mM	0.90 (0.61-1.31)	0.58		
Body mass index, per 1 kg/m^2	1.04 (0.94-1.14)	0.45		
Chronic kidney disease	2.39 (1.10-5.20)	0.03	2.23 (1.02-4.89)	0.04
Estimated glomerular filtration rate, 1 mL/min/1.73 m^2	0.99 (0.97-1.02)	0.60		
Hematocrit, per 10%	1.44 (0.52-4.00)	0.48		
Smoking habits	1.71 (0.73-4.01)	0.22		
Alcohol intake	0.74 (0.34-1.61)	0.44		

Multivariate model included age, sex, diastolic blood pressure, and chronic kidney disease.

TABLE 4. Association of Diastolic Pressure and Chronic Kidney Disease (CKD) with the Development of RVO by Hypertension Status: The Hisayama Study, 1998-2007

Group	Crude Incidence of RVO: Population at Risk (*n*)	Crude Incidence of RVO: Cases *n* (%)	Age- and Sex-Adjusted Odds Ratio (95% Confidence Interval)	*P*	*P* for Heterogeneity
Hypertension(−)					
Diastolic blood pressure, per 10 mm Hg	805	18 (2.2)	1.41 (0.72-2.77)	0.31	
Hypertension(+)					
Diastolic blood pressure, per 10 mm Hg	564	23 (4.1)	1.58 (1.03-2.42)	0.034	0.69
Hypertension(−)					
Non-CKD	745	15 (2.0)	1		
CKD	60	3 (5.0)	1.79 (0.48-6.74)	0.38	
Hypertension(+)					
Non-CKD	478	16 (3.3)	1		
CKD	86	7 (8.1)	2.86 (1.07-7.63)	0.035	0.99

The present study found that higher diastolic blood pressure was significantly associated with RVO and that higher systolic blood pressure was marginally associated with RVO. The risk of elevated diastolic blood pressure for RVO was higher in both the hypertensive and the nonhypertensive groups (*P* for heterogeneity = 0.69), indicating the close association of diastolic blood pressure and RVO. Although the etiology and pathogenesis of RVO are largely unknown, the consistent association with elevated blood pressure found in this study is in accordance with the findings from many other studies,[6-8,10-12] confirming the blood pressure–related nature of the disease. In contrast, the baseline hypertension was not significantly associated with RVO. This may, in part, occur because of receiving antihypertensive medication in hypertensive persons. This suggests that uncontrolled hypertension may be a more important contributing factor to RVO. Therefore, subjects with elevated blood pressure should be considered a high-risk population of RVO. Strict control of elevated blood pressure may be important in preventing the disease.

We found that a CKD was associated with RVO, independent of age, sex, and diastolic blood pressure. Previously only two population-based cohort studies have reported on the association between renal dysfunction and RVO, and the results have been inconsistent. In the Blue Mountains Eye Study, the serum creatinine level was not associated with the development of RVO in a 10-year follow-up period.[8] On the other hand, higher serum creatinine levels constituted a significant risk factor for RVO over 15 years of follow-up in the Beaver Dam Eye Study; persons with elevated creatinine levels (≥1.4 mg/dL) were shown to have a 60% higher risk of RVO.[16] In our study, CKD increased the risk of developing RVO by 2.2-fold even after adjustment for other confounding factors. These discrepancies in the association between renal dysfunction and RVO may be partly due to differences in ethnicity, study populations, or study methods. One possible reason is that serum creatinine, which was used as a measure of renal function in both the Blue Mountains Eye Study and the Beaver Dam Eye Study, is less sensitive than eGFR, which was used in our study, in the detection of small differences in the levels of kidney function; thus, an association in low-risk general populations may be less detectable when serum creatinine is used. After all, our findings provide important evidence of a link between CKD and RVO and suggest that CKD affects ocular circulation.

Renal dysfunction and RVO are both closely related to hypertension.[6,21] This fact indicates concomitant damage in the retinal and renal vasculature by hypertension. In this study, however, CKD was an independent risk factor for the development of RVO, even after adjustment for age, sex, and diastolic blood pressure. We also demonstrated that the risk of RVO is higher in subjects with CKD than that in subjects without CKD in both the nonhypertension and the hypertension groups (*P* for heterogeneity = 0.99). These findings suggest that CKD was an independent risk factor for the development of RVO regardless of hypertension status, and that hypertension is not a key factor connecting CKD and RVO. It is well recognized that renal arteriosclerosis and glomerular sclerosis are closely related to systemic atherosclerosis.[22] Our previous population-based autopsy study of Hisayama residents also indicated that CKD was significantly associated with the severity of coronary atherosclerosis.[23] Based on these findings, it is speculated that CKD is a strong risk factor for systemic arteriosclerosis, including retinal arteriosclerosis, and that retinal sclerotic arteriolar walls may compress the underlying veins at arteriovenous crossings, leading to reduced blood flow, which in turn could facilitate the development of a thrombus and downstream venous occlusion and thereby of RVO.

The several strengths of our study include its longitudinal population-based design, long follow-up, and masked grading of retinal photographs from both eyes after pupil dilatation. However, several limitations merit consideration. First, we calculated eGFR levels using the IDMS-MDRD study equation with a single measure of serum creatinine. This may have caused some degree of misclassification of eGFR levels. Given that this limitation can reduce the impact of RVO, the true association may be stronger than that shown in our findings. Second, we ascertained RVO cases by using one photographic field per eye, whereas in most previous population-based studies, at least two photographic fields were taken per eye. This could have resulted in underestimation of the prevalence of RVO in our study, if peripheral lesions were overlooked. However, we diagnosed RVO with fundus examinations by indirect ophthalmoscopy, slit-lamp, and color fundus photographs in both eyes after pupil dilatations. Therefore, RVO could be diagnosed with accuracy.

In conclusion, our findings suggest that the incidence of RVO is higher in Japanese than that in other Asians and Caucasians, and that higher blood pressure and CKD are independent risk factors for the development of RVO in the general Japanese population. Therefore, subjects having elevated blood pressure or CKD should be considered a high-risk population of RVO.

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Prevalence and Systemic Risk Factors for Retinal Vein Occlusion in a General Japanese Population: The Hisayama Study

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Purpose. To examine the prevalence of retinal vein occlusion (RVO) and its systemic relevant factors in a general Japanese population aged 40 years or older.

Methods. In 1998, 1775 Hisayama residents consented to participate in the study. Each participant underwent a comprehensive examination that included ophthalmic testing. RVO was determined by grading color fundus photographs. Logistic regression analysis was performed to determine risk factors for RVO.

Results. Of the 1775 subjects examined, 38 had RVO. The prevalence of RVO was 2.1% (2.0% for branch RVO and 0.2% for central RVO). After adjustment for age and sex, it was found that systolic and diastolic blood pressures, hypertension, and hematocrit were significantly associated with RVO. In multivariate analysis, age (per 10 years; odds ratio [OR], 1.47; 95% confidence interval [CI], 1.04–2.08), hypertension (OR, 4.25; 95% CI, 1.82–9.94), and hematocrit (per 10%; OR, 3.09; 95% CI, 1.10–1.22) remained independently significant risk factors for RVO. Both high-normal blood pressure and hypertension were significantly associated with RVO. Furthermore, compared with normotensive subjects without high hematocrit, the likelihood of RVO was markedly high in subjects having both high blood pressure and high hematocrit (age- and sex-adjusted OR, 36.0; 95% CI, 4.43–292).

Conclusions. The findings suggest that the prevalence of RVO is higher in the Japanese than in other Asians or Caucasians and that older age, higher hematocrit, and both hypertension and high-normal blood pressure are significant risk factors for RVO in the Japanese. (*Invest Ophthalmol Vis Sci.* 2010;51:3205–3209) DOI:10.1167/iovs.09-4453

Retinal vein occlusion (RVO) is a cause of significant loss of vision in elderly populations in developed countries.[1] Despite the magnitude of this problem, the available treatment options remain limited.[2,3] Furthermore, RVO has also been associated with increased risk of cardiovascular disease.[4–6] In developing measures to prevent this disease, it is thus very important to determine the prevalence of RVO and to identify its systemic risk factors. To date, several population-based studies,[6–11] mostly in Caucasian populations, have provided valuable information on the prevalence and systemic risk factors for RVO. These include hypertension,[6–11] diabetes,[10] smoking habits,[10] dyslipidemia,[7,9] and a history of angina.[9] However, there have been only a limited number of population-based epidemiologic studies on RVO in Japanese and other Asians.[9,11,12]

The purpose of this article was to examine the prevalence of RVO and its systemic relevant factors in a cross-sectional study of a general Japanese population.

Methods

Study Population

The Hisayama Study is an ongoing long-term prospective cohort study on cardiovascular disease and its risk factors in Hisayama, a town adjoining Fukuoka City, a metropolitan area in southern Japan.[13,14] As a part of the follow-up survey, we performed a cross-sectional examination, including an eye examination, of Hisayama residents aged 40 years or older in 1998.[15] Among 4187 residents in that age group, 1775 (42.4%; 688 men and 1087 women) were enrolled in the present study.

Ophthalmic Examination and Definition of RVO

The methods used for the ophthalmic examination have been published in detail.[15] Briefly, each participant underwent a comprehensive ophthalmic examination, including a stereoscopic fundus examination with indirect ophthalmoscopy and examination with a slit-lamp biomicroscope with a superfield lens (Volk, Mentor, OH), after pupil dilation with 1.0% tropicamide and 5% phenylephrine. Fundus photographs (45°) were taken of both eyes of each participant with a nonmydriatic fundus camera (TRC NW-5; Topcon, Tokyo, Japan) and slide film (Fujichrome Sensia II; Fujifilm, Tokyo, Japan). We photographed one field, centered at a point midway between the temporal edge of the optic disc and the fovea in both eyes. The presence of RVO was determined based on the grading of fundus examinations by indirect ophthalmoscopy and slit lamp and the color fundus photographs. All photographs were evaluated by retinal specialists (MY and TI) who were masked to the participants' data. The presence or absence of central or branch RVO was defined according to a standardized protocol.[6,10,16] Recent central RVO was characterized by retinal edema, optic disc hyperemia or edema, scattered superficial and deep retinal hemorrhages, and venous dilation. Old central RVOs were characterized by occluded and sheathed retinal veins or vascular anastomosis at the optic disc. Branch RVOs involved a more localized area of the retina in the sector of the obstructed venule and were characterized by scattered superficial and deep retinal hemorrhages, venous dilation, intraretinal microvascular abnormalities, and occluded and sheathed

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