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ORIGINAL ARTICLE

Intrarenal arterial resistance is associated with microvascular complications in Chinese type 2 diabetic patients

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ABSTRACT

Background. Increased renal arterial resistance is associated with various types of chronic renal parenchymal diseases. A resistance index (RI) >0.8 predicts deterioration in renal function in diabetic subjects. However, the association between renal RI and other diabetic complications has not been investigated. In this study, we examined the association between intrarenal arterial RI and diabetic complications in Chinese type 2 diabetic subjects.

Methods. Three hundred and eighty-seven Chinese type 2 diabetic patients were recruited from a structured assessment programme to evaluate their risk factors and complications as a part of the quality improvement programme at the Prince of Wales Hospital. All subjects underwent ultrasound examinations for the assessment of intrarenal arterial RI of both kidneys. Clinical and biochemical parameters, including diabetes-related microvascular complications (nephropathy, retinopathy and sensory neuropathy) and macrovascular diseases, were examined.

Results. The mean RI of patients with any microvascular complications (0.70 ± 0.09 versus 0.65 ± 0.06) such as nephropathy (0.71 ± 0.09 versus 0.66 ± 0.06), retinopathy (0.71 ± 0.08 versus 0.67 ± 0.08) and sensory neuropathy (0.75 ± 0.07 versus 0.68 ± 0.08) and with any macrovascular complications (0.71 ± 0.09 versus 0.68 ± 0.08) was higher than those without ($P < 0.05$). On multivariate analysis, after controlling for confounding variables, an RI ≥0.75 was associated with microvascular complications, nephropathy, retinopathy and sensory neuropathy, with odds ratio of 4.02 [95% confidence interval (CI) 1.72–9.4], 4.99 (2.61–9.56), 2.78 (1.52–5.09) and 5.74 (1.8–18.3), respectively. The association of RI with macrovascular complications was not significant in multivariate analysis.

Conclusion. Increased intrarenal arterial resistance was independently associated with an increased risk of microvascular complications including diabetic nephropathy, diabetic retinopathy and diabetic sensory neuropathy in Chinese type 2 diabetic patients.

INTRODUCTION

The resistance index (RI) of the kidneys as assessed by real-time Doppler ultrasound is associated with a worsening of renal function [1], various types of renal diseases [2–4] and increased mortality [5]. In diabetic subjects, an RI is associated with diabetic nephropathy [6–8] and chronic kidney disease [9] and furthermore predicts deterioration of renal function [10]. There are close, albeit not invariable, associations among nephropathy, retinopathy and neuropathy in diabetes subjects, and this is possibly due to risk factors or mediators that they have in common [11–13]. To our knowledge, there have not been any previous studies that investigated the association between RI and diabetic complications, with the exception of diabetic nephropathy.

In this study, we examined the relationship between RI and microvascular complications (nephropathy, retinopathy and sensory neuropathy) and macrovascular complications (peripheral vascular disease [PVD], cerebrovascular events, myocardial infarction, angina and heart failure requiring hospitalization and revascularization procedures) in Chinese type 2 diabetes subjects.

MATERIALS AND METHODS

Three hundred and eighty-seven Chinese type 2 diabetic patients (228 men and 159 women) were recruited from a structured complication screening programme at the Diabetes and Endocrine Centre at the Prince of Wales Hospital. One hundred and thirteen subjects of the 387 recruited subjects were reported in a previous study investigating the association of RI with chronic kidney disease [9]. Patients undergoing comprehensive clinical assessment were invited to participate in the study, depending on the availability of ultrasound examination during the week of recruitment. The study was approved by the local institutional clinical research ethics committee with written informed consent obtained from each participant. Exclusion criteria included recipients of renal allograft and a known history of renal artery stenosis defined as a 50% reduction or more in luminal diameter of the renal artery. The subjects with evidence of hydronephrosis on grey-scale ultrasound or arrhythmia (indicating bradycardia or tachycardia) on Doppler ultrasound examination were also excluded.

Ultrasound measurements of RI

Real-time Doppler ultrasound examination was performed using the Philips ATL HDI 5000 ultrasound machine and C5-2 curvillinear transducer. The subjects lie in the supine position for a general check to rule out significant renal abnormality such as hydronephrosis. Then the subjects turned 30° to the left and then to the right sides for the scanning of the intrarenal arteries of right and left kidneys, respectively. The oblique positions of the subjects could allow the ultrasound tranducers to align the long axis of the intrarenal vessels, and this could facilitate the correct angle correction for Doppler measurement. The interlobar arteries of the mid-poles of both kidneys were identified with colour applications of the ultrasound machine, and Doppler measurements were made one to three times. The Doppler spectrum with the most stable velocity tracing was used for analysis. The Doppler spectra were obtained with a sample size of 1 mm. The RI [(peak systolic velocity − end-diastolic velocity)/peak systolic velocity] was measured with electronic calipers. The RI was not measured in the upper and lower poles of the kidneys in this study because the RI difference among different poles of the kidneys is very small ranging from 0.3 to 1.5% as shown in the first 113 subjects (unpublished data). The mean value of the RI measurements from both sides was used for analysis. Two experienced sonographers (with 20 and 12 years of experience in ultrasonography) performed the ultrasound scanning and Doppler measurements. The two operators also performed repeated scans in 10 subjects for the reliability study of the RI measurements, and the intraclass correlation coefficients for interoperator and intraoperator variabilities were 0.97 (95% CI 0.87–0.99) and 0.94 (0.77–0.98), respectively.

Clinical assessment

All patients underwent a comprehensive clinical evaluation using a structured protocol conducted by trained personnel, which was modified from the European DIABCARE protocol [14–17]. Measured parameters included body mass index, sitting blood pressure after at least 5 min of rest, visual acuity, fundoscopy by retinal camera, foot examination using Doppler scan and monofilament and graduated tuning fork. All fundus photos were read by endocrinologists or trained doctors. Retinopathy was defined as the presence of dot and blot haemorrhages, hard exudates, cotton wool spots, neovascularization, laser scars or a history of vitrectomy. Diabetic nephropathy was defined as a urinary albumin:creatinine ratio ≥3.5 mg/mmoL [18]. PVD was defined by the absence of foot pulse on palpation and confirmed by the ankle-

brachial index measurement of <0.9. Sensory neuropathy was defined by the presence of two of the following three criteria: reduced sensation to monofilament examination in any part of the sole with normal skin, a score of ≤6/8 (age <65 years) or ≤4/8 (age >65 years) using a graduated tuning fork or typical symptoms of numbness and abnormal sensation over lower limbs clinically suggestive of diabetic neuropathy. Microvascular complications were defined as the presence of nephropathy, retinopathy and/or sensory neuropathy. Macrovascular complications were defined as PVD, a history of cerebrovascular events, myocardial infarction, revascularization procedures and/or angina and heart failure requiring hospitalization [15, 19].

Fasting blood samples were taken for the measurement of plasma glucose, lipid profiles, renal function and glycated haemoglobin (HbA_{1C}). Random spot sterile urine samples were collected to document any evidence of diabetic nephropathy.

Statistical analysis

All data are expressed as mean ± standard deviation. Diabetes duration, triglycerides and HbA_{1C} were logarithmically transformed due to its skewed distribution. Analysis of variance (ANOVA) or Chi-square tests were performed to compare the mean values and frequencies among subjects with different RI. Independent *t*-tests for two independent samples were used to compare the mean RI between the subjects with and without diabetic complications. Multiple stepwise logistic regressions were performed to evaluate the relationships between various diabetic complications and RI (both as a continuous variable and categories stratified by $RI < 0.7$, $0.7 \leq RI < 0.75$, $RI \geq 0.75$ in different statistical models), sex, age, diabetes duration, HbA_{1C}, smoking status, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, pulse pressure (systolic blood pressure–diastolic blood pressure), use of antihypertensive medication and body mass index as independent variables. History of cardiovascular diseases including heart disease, stroke or PVD was categorized as macrovascular diseases and analysed as a group due to the small number of affected subjects.

Results

Table 1 shows the clinical characteristics of the participants with a mean age of 58.3 ± 11.8 years and mean disease duration of 11.1 ± 7.8years. In this study, approximately 65% of patients had at least one microvascular complication and 15% had at least one macrovascular event. Subjects with high RI were older, had higher blood pressure measurements, a greater degree of renal impairment and were more likely to have micro- and macrovascular complications. There were no significant differences in body mass index, glycaemic indices and lipid profiles between subject groups of different RI. In addition, the mean RI values of right and left kidneys were 0.68 and 0.66, with difference < 3%.

Association of RI with diabetic complications

On univariate analysis, the mean RI values were higher in subjects with microvascular complications, including diabetic nephropathy, diabetic retinopathy or diabetic sensory neuropathy, and in subjects with macrovascular complications than those without (Table 2). In the multivariable stepwise logistic regression model with RI as continuous variable, RI was independently associated with microvascular complications, including diabetic nephropathy, diabetic retinopathy and diabetic sensory neuropathy after controlling for confounding variables (Table 3). In the multivariate stepwise logistic regression with RI as a categorical variable, $RI \geq 0.75$ was associated with microvascular complications, diabetes-related nephropathy, retinopathy and sensory neuropathy when compared with the reference value of $RI < 0.7$ (Table 4). There was no significant association between RI and macrovascular complications in the logistic regression models, after adjustment for confounders. The diabetes duration was also found to be associated with microvascular complications, diabetic retinopathy and neuropathy, while the use of antihypertensive drug was associated with microvascular complications, diabetic nephropathy and macrovascular complications.

DISCUSSION

In Chinese type 2 diabetic patients, there were independent associations between RI and microvascular complications, including diabetes-related nephropathy, retinopathy and sensory neuropathy, but not with macrovascular complications. An RI of ≥0.75 was associated with a 2.8–5.7-fold increase in the risk for all microvascular complications, particularly diabetic nephropathy and diabetic neuropathy, when compared with the reference value. Although macrovascular complications were associated with an increased RI on univariate analysis, this was lost after controlling for blood pressure, diabetes duration, glycated haemoglobin and lipid profile. The diabetes duration was associated with microvascular complications, including diabetic retinopathy and neuropathy, which was in keeping with previous findings [20]. The long duration of diabetes is a significant risk factor for advanced arteriosclerosis [21], which may contribute to vascular complications. The RI is also partially dependent on antihypertensive medications [22], and both still had an independent association with microvascular complications including diabetic nephropathy.

The use of RI to assess renal disease and associated clinical conditions has been well established. In hypertensive subjects, an RI of ≥0.7 was associated with high blood pressure, increased carotid intima-media thickness, left ventricular mass index and diastolic dysfunction [23]. Other centres have used $RI \geq 0.7$ to differentiate between normal and non-obstructive renal diseases [2–4]. In patients with chronic kidney disease, RI correlated with serum creatinine and reduced renal clearance [24]. The vascular stiffness of central arteries as reflected

Table 1. The demographic information and clinical parameters of the study subjects with different categories of renal resistance indices

	All (n = 387)	RI < 0.7 (n = 228)	0.7 ≤ RI < 0.75 (n = 73)	0.75 ≤ RI < 0.8 (n = 54)	RI ≥ 0.8 (n = 32)	P-values
Age (years)	58.3 ± 11.8	53.6 ± 10.6	61.9 ± 9.5	66.6 ± 9.9	69.3 ± 9.9	< 0.001
Body mass index (kg/m^2)	26.2 ± 4.7	26.3 ± 5.0	26.2 ± 3.9	26.0 ± 5.0	26.1 ± 2.7	0.99
Diabetes duration (years)	11.1 ± 7.8	8.3 ± 6.2	12 ± 7.4	17.4 ± 7.0	18.9 ± 8.6	< 0.001
HbA_{1C} (%)	7.4 ± 1.63	7.26 ± 1.69	7.61 ± 1.65	7.77 ± 1.66	7.3 ± 0.87	0.14
Total cholesterol (mmol/l)	4.53 ± 0.90	4.57 ± 0.90	4.61 ± 0.93	4.44 ± 0.96	4.25 ± 0.74	0.19
HDL-cholesterol (mmol/l)	1.27 ± 0.32	1.28 ± 0.33	1.29 ± 0.31	1.27 ± 0.34	1.14 ± 0.23	0.14
LDL-cholesterol (mmol/l)	2.49 ± 0.78	2.52 ± 0.75	2.59 ± 0.85	2.43 ± 0.82	2.26 ± 0.69	0.21
Triglycerides (mmol/l)	1.81 ± 1.46	1.83 ± 1.62	1.77 ± 1.40	1.71 ± 1.06	1.95 ± 0.98	0.88
Systolic blood pressure (mmHg)	137.1 ± 20.2	131.5 ± 17.5	140.6 ± 20.9	147.2 ± 21.2	151.5 ± 19.9	< 0.001
Diastolic blood pressure (mmHg)	82.3 ± 10.3	83.2 ± 10.4	81.7 ± 10.4	81.9 ± 10.0	77.5 ± 9.48	0.033
Plasma creatinine	85.2 ± 48.6	75.8 ± 30.9	78.1 ± 39.7	110.7 ± 69.5	125 ± 83.4	< 0.001
Antihypertensive drug (n, %)	289 (74.7)	151 (66.2)	57 (78.1)	49 (90.7)	32 (100)	< 0.001
CCB (n, %)	154 (39.8)	68 (29.8)	30 (41)	31 (57.4)	25 (78.1)	< 0.001
β-Blockers (n, %)	106 (27.4)	50 (21.9)	16 (21.9)	20 (37)	20 (62.5)	< 0.001
Diuretics (n, %)	49 (12.7)	21 (9.2)	7 (9.6)	11 (20.4)	10 (31.3)	0.001
ACEI/ARB (n, %)	227 (58.7)	115 (50.4)	46 (63)	39 (72.2)	27 (84.4)	< 0.001
Microvascular complications (%)	251 (64.9)	128 (56.1)	45 (61.6)	49 (90.7)	29 (90.6)	< 0.001
Nephropathy (%)	184 (47.5)	82 (36)	32 (43.8)	41 (75.9)	29 (90.6)	< 0.001
Retinopathy (%)	151 (39)	67 (29.4)	32 (43.8)	35 (64.8)	17 (53.1)	< 0.001
Neuropathy (%)	24 (6.2)	6 (2.6)	2 (2.7)	12 (22.2)	4 (12.5)	< 0.001
Macrovascular complications (%)	61 (15.8)	31 (13.6)	10 (13.7)	10 (18.5)	10 (31.2)	0.068

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HDL, high density lipoprotein; LDL, low-density lipoprotein.
P-values were based on ANOVA or Chi-square tests as appropriate.

Table 2. The mean RI and P-values (based on independent *t*-test) in the patients with and without diabetic complications

	RI in positive group	RI in negative group	P-values
Microvascular complications	0.70 ± 0.09	0.65 ± 0.06	< 0.001
Nephropathy	0.71 ± 0.09	0.66 ± 0.06	< 0.001
Retinopathy	0.71 ± 0.08	0.67 ± 0.08	< 0.001
Neuropathy	0.75 ± 0.07	0.68 ± 0.08	< 0.001
Macrovascular complications	0.71 ± 0.09	0.68 ± 0.08	0.013

Table 3. Multiple stepwise logistic regression with various diabetic complications as dependent variables in different statistical models

Dependent variables	Significant independent variables	P-values	Odds ratio	95% Confidence interval
Microvascular complications	RI (×10)	0.004	1.7	1.19–2.43
	Log(diabetes duration)	0.034	2.09	1.06–4.12
	Log(HbA_{1C})	0.034	25.8	1.29–519.8
	HDL-C	0.001	0.28	0.13–0.59
	Antihypertensive drug	0.003	2.26	1.31–3.88
Nephropathy	RI (×10)	< 0.001	1.89	1.38–2.59
	BMI	0.039	1.06	1.0–1.12
	Log (HbA_{1C})	0.005	53.8	3.26–868.1
	Antihypertensive drug	< 0.001	5.81	2.98–11.3
Retinopathy	RI (×10)	0.002	1.65	1.21–2.26
	Sex (male)	0.019	1.74	1.1–2.78
	Log (diabetes duration)	0.005	2.56	1.33–4.94
Neuropathy	RI (×10)	0.005	2.39	1.31–4.39
	Sex (male)	0.001	7.65	2.27–25.8
	Log (diabetes duration)	0.02	8.42	1.39–51
Macrovascular complications	Sex (male)	0.013	2.34	1.2–4.56
	Age	0.002	1.05	1.02–1.08
	HDL-C	0.011	0.23	0.073–0.71
	Antihypertensive drug	0.036	3.18	1.01–9.38

The independent variables include sex, age, body mass index (BMI), log(diabetes duration), smoking history, log(HbA_{1C}), systolic and diastolic blood pressure, pulse pressure, total cholesterol, HDL-cholesterol, log(triglycerides) and use of antihypertensive drug and RI (as continuous variable).

Table 4. Multivariate stepwise logistic regression with various diabetic complications as dependent variables in different statistical models

Dependent variables	Significant independent variables	P-values	Odds ratio	95% Confidence interval
Microvascular complications	RI < 0.7	0.003		
	0.7 ≤ RI < 0.75	0.79	0.92	0.5–1.69
	RI ≥ 0.75	0.001	4.02	1.72–9.4
	Log (diabetes duration)	0.05	1.99	1.0–3.96
	Log (HbA_{1C})	0.017	40.2	1.95–829.1
	HDL-C	0.001	0.28	0.13–0.6
	Antihypertensive drug	0.004	2.24	1.3–3.85
Nephropathy	RI < 0.7	< 0.001		
	0.7 ≤ RI < 0.75	0.85	1.06	0.58–1.94
	RI ≥ 0.75	< 0.001	4.99	2.61–9.56
	BMI	0.033	1.06	0.58–1.94
	Log (HbA_{1C})	0.003	80.4	4.64–1391
	Antihypertensive drug	< 0.001	5.55	2.83–10.9
Retinopathy	RI < 0.7	0.002		
	0.7 ≤ RI < 0.75	0.031	1.92	1.06–3.47
	RI ≥ 0.75	0.001	2.78	1.52–5.09
	Sex (male)	0.016	1.79	1.11–2.86
	Log (diabetes duration)	0.006	2.5	1.3–4.83
Neuropathy	RI < 0.7	0.004		
	0.7 ≤ RI < 0.75	0.96	0.96	0.18–5.18
	RI ≥ 0.75	0.003	5.74	1.8–18.3
	Sex (male)	0.001	7.04	2.16–23
	Log (diabetes duration)	0.036	7.48	1.14–49.2
Macrovascular complications	Sex (male)	0.013	2.34	1.2–4.56
	Age	0.002	1.05	1.02–1.08
	HDL-C	0.011	0.23	0.07–0.71
	Antihypertensive drug	0.036	3.18	1.08–9.38

The independent variables include sex, age, body mass index (BMI), log(diabetes duration), smoking history, log (HbA_{1C}), systolic and diastolic blood pressure, pulse pressure, total cholesterol, HDL-cholesterol, log(triglycerides) and use of antihypertensive drug and RI (categorized as RI < 0.7, 0.7 ≤ RI < 0.75 and RI ≥ 0.75).

by the pulse wave velocity, pulse pressure and intima-media thickness would also affect the renal resistance [25].

In newly diagnosed patients with renal disease, an RI of ≥0.8 is predictive of future deterioration of renal function, progression to dialysis therapy and all-cause mortality [1]. However, in elderly subjects who underwent renal Doppler scan, end-diastolic frequency rather than RI predicted adverse cardiovascular events [26]. The end-diastolic

frequency is subject to greater variation due to the Doppler angle effect and is less reproducible when compared with RI measurements. So end-diastolic frequency measurement was not commonly used and not attempted in this study.

Diabetes is associated with generalized vasculopathy with a high incidence of renal dysfunction [27]. In diabetes, RI is associated with the progression of diabetic nephropathy independent of albuminuria [28], diastolic dysfunction [29], insulin resistance [30] and non-albuminuric renal insufficiency [8]. Our group has previously validated the use of an RI $\geq$ 0.75 as the optimal cut-off value to identify chronic kidney disease which was also associated with increased carotid intima-media thickness [9].

Despite the frequent coexistence of micro- and macrovascular complications, their associations with RI have not been studied. In this study, we categorized subjects using RI values of < 0.7, $\geq$ 0.7 to < 0.75, $\geq$ 0.75 to < 0.8 and $\geq$ 0.8, which have been reported to correlate with normal kidneys, renal dysfunction [2–4], chronic kidney disease [9], renal deterioration and all-cause mortality, respectively [1]. In the multivariate analysis, due to the small number of affected subjects, we combined subjects with RI $\geq$ 0.8 to those with RI values of $\geq$0.75 to <0.8 as a single group for analysis.

The RI reflects the vascular flow resistance in the small arteries, arterioles and capillaries in the renal parenchyma. The mechanism underlying this increased RI is not fully understood as yet. The non-specific scarring process characterized by interstitial fibrosis, loss of capillaries and glomeruli can lead to the reduced number of intrarenal vessels and filtration area [1] and to increased parenchymal vascular resistance. Besides diabetic glomerulopathy, arteriosclerotic and tubulointerstitial lesions often occur, which can contribute to intrarenal resistance [6]. Diabetes is a strong risk factor for arteriosclerosis [20], which is systemic in nature and may affect arteries of different size [31]. However, the extent and severity vary among arteries of different size [32]. This may partially explain the different associations of RI with micro- and macrovascular complications in this study. However, the lack of the association of RI with macrovascular complications in this study might be in part due to the small number of affected subjects. Furthermore, study with a larger sample size is required to confirm the relationships of RI with macrovascular complications.

In this study, besides indicating a perturbation of microvascular flow in the kidney, RI may also reflect abnormal flow in other vascular beds, notably in the retina and nerves. In this regard, microvasculature abnormalities in retinal photography were associated with subclinical and clinical manifestation of cardiovascular disease [33, 34] as well as impaired myocardial perfusion after coronary revascularization procedures [35]. Taken together, the close associations of RI with microvascular complications highlight the importance of generalized vasculopathy in diabetes. The fact that RI is still associated with these complications after controlling for conventional risk factors suggests that other unmeasured causes or mediators (e.g. oxidative stress and inflammation) may be contributing to these associations [36]. There is a close association between inflammatory markers (including interleukin-6 and tumour necrosis factor-α) and diabetes [37], and the inflammation may play a linking role for the association among diabetes, vascular complications and RI. By using RI, we may be able to identify high-risk subjects who require more intensive therapy.

Study limitations

Our study was not without limitations. This was a cross-sectional observational study and prospective evaluation will be needed to confirm the predictive value of RI to identify high-risk subjects for intervention.

Conclusion

In Chinese type 2 diabetic patients, an RI of $\geq$0.75 is associated with a 2.8–5.7-fold risk for microvascular complications independent of conventional risk factors.

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CONFLICT OF INTEREST STATEMENT

None declared.

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