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Original Article

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Association of Flow Parameters and Diameter in the Common Carotid Artery with Impaired Glucose Metabolism

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Aim: Diameter, intima–media thickness (IMT), and flow parameters, including resistance index (RI) and pulsatility index (PI), in the common carotid artery (CCA) are markers of arterial remodeling, atherosclerosis, and vascular resistance, respectively. We investigated the differences among these markers in association with plasma glucose level, serum insulin level, and insulin resistance in participants without cardiovascular disease.

Methods: CCA parameters (including the CCA interadventitial diameter and mean IMT at the time of 75-g oral glucose tolerance testing) were assessed in 4218 participants. RI and PI were assessed in 3380 of these participants. To assess plasma glucose and serum immunoreactive insulin profiles during oral glucose tolerance testing, we used the total areas under the curves (AUCglu and AUCins, respectively). We used the homeostasis model assessment of insulin resistance (HOMA-IR) and the Matsuda index to assess insulin resistance. Insulin secretion was assessed with the HOMA-β.

Results: AUCglu was significantly associated with CCA interadventitial diameter ($\beta=0.048$, $P<0.001$), RI ($\beta=0.144$, $P<0.001$), and PI ($\beta=0.103$, $P<0.001$) but not with mean IMT. AUCins ($\beta=-0.064$, $P<0.001$) and HOMA-β ($\beta=-0.054$, $P<0.001$) were significantly and negatively associated with CCA interadventitial diameter, but not with mean IMT. Both HOMA-IR and Matsuda index were significantly associated with RI and PI.

Conclusions: These findings indicate that all CCA parameters except IMT are associated with impaired glucose metabolism in patients without cardiovascular disease.

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Key words: Carotid artery diameter, Intima–media thickness, Insulin resistance, Pulsatility index, Resistance index

Introduction

The common carotid artery (CCA) is part of the elastic arterial tree, and CCA parameters, including diameter and intima–media thickness (IMT), are noninvasively assessed by ultrasonography[1]. CCA diameter has been associated with serum brain natriuretic peptide level[2], left ventricular hypertrophy, urinary albumin/creatinine ratio[3], and the severity of coronary artery disease[4]. Several investigators have reported that CCA diameter is predictive of cardiovascular events and mortality[5-7]. Their evidence may be based partly on the CCA diameter as a marker of arterial remodeling[8, 9]. Insulin resistance and impaired glucose metabolism contribute to arterial remodeling through several intermediate pathways[10]. However, available data regarding the association of insulin resistance, plasma glucose level, and serum

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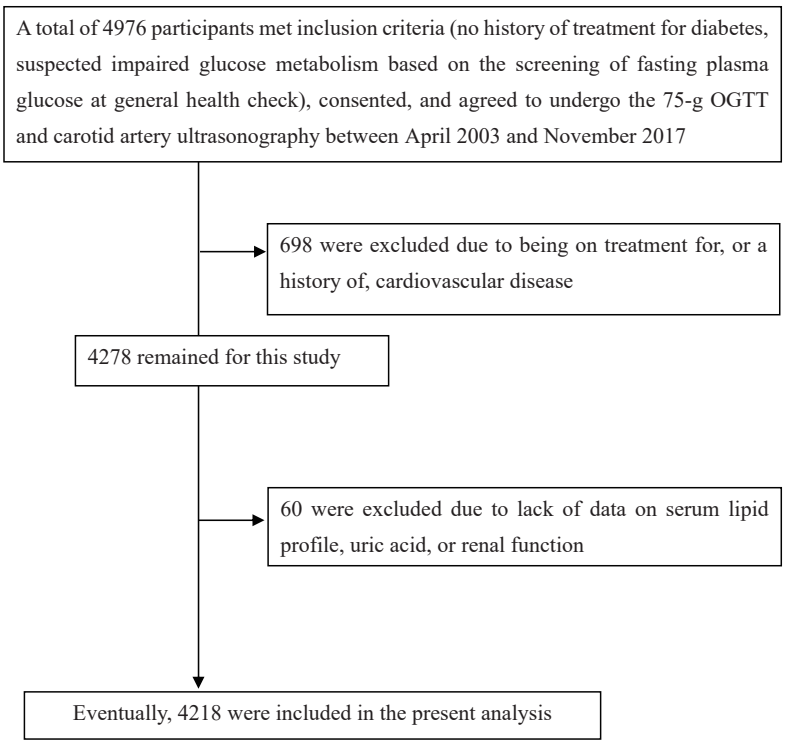

Fig. 1. Flowchart for participant selection
Abbreviations: OGTT, oral glucose tolerance testing

insulin level with CCA diameter are limited[11, 12]. The IMT is widely used as a marker of atherosclerosis[13] and is a predictor of cardiovascular disease (CVD) in individuals with type 2 diabetes[14]. However, in previous studies, results regarding the associations between IMT and both plasma glucose level and insulin resistance have been inconsistent[15-20]. Furthermore, the association of CCA flow parameters, including resistance index (RI) and pulsatility index (PI)[21], with impaired glucose metabolism has not been well studied. The RI and PI of the CCA reflect vascular resistance of small blood vessels in cerebral arterial trees distal to the measurement point in the CCA[22]; therefore, these parameters may represent microvascular damage resulting from impaired glucose metabolism.

Aim

In this study, we aimed to investigate the association of plasma glucose and serum insulin levels and insulin resistance with CCA diameter, IMT, RI, and PI in a large-scale population without CVD, and sought to clarify the differences in these CCA parameters in association with impaired glucose metabolism.

Methods

Study Population

We used data from the Hiroshima Study on Glucose Metabolism and Cardiovascular Diseases (Hiroshima GMCVD). This cross-sectional and longitudinal study examined the inter-relationship among impaired glucose metabolism, hypertension, and CVD[23, 24]. Details about participants in the Hiroshima GMCVD were described previously[23]. Of the 4976 participants who underwent 75-g oral glucose tolerance testing (OGTT) and carotid artery ultrasonography at the Health Management and Promotion Center of Hiroshima Atomic Bomb Casualty Council between April 2003 and November 2017, 698 were excluded because they were on treatment for, or had a history of, CVD (including coronary heart disease and stroke). Another 60 were excluded because their baseline data were incomplete (e.g., values for serum lipid profile, uric acid, and renal function were missing; **Fig. 1**). We asked all participants about their regular medications and medical histories during the general health checkups, including treatment for hypertension and dyslipidemia, and about their drinking and smoking habits.

We obtained written informed consent from all

participants during their health checkups. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The Hiroshima Atomic Bomb Casualty Council Committee on the Ethics of Human Research provided ethical approval for this study. This study was registered under the UMIN protocol registration system (ID: UMIN000036648).

Carotid Artery Ultrasonographic Measurements

A team of experienced echographers who were blinded to the purpose of the study performed carotid artery ultrasonography, using standard techniques with an HDI 3500 Diagnostic Ultrasound System (Advanced Technology Laboratories Ultrasound, Inc., Washington, U.S.A.) and a HI VISON Preirus (Hitachi Medical Corporation, Tokyo, Japan) equipped with a 7.5-MHz linear-array transducer at the time of 75-g OGTT. Each participant was examined in the supine position with the head turned 45° from the site being scanned. CCA interadventitial diameter was measured during the late phase of vascular contracting (end-diastolic phase) on the longitudinal scan at a point 10-mm proximal from the beginning of the carotid bulb. The CCA interadventitial diameter was the distance between the adventitia–media interface on the near wall and the media–adventitia interface on the far wall. The IMT was defined as the distance between the lumen–intima and media–adventitia interfaces. To determine the greatest IMT, the CCA was scanned in the longitudinal axis view, and at the IMT was measured 10 mm proximal and 10 mm distal to the site of the greatest IMT. Then, the mean IMT values at these three points was calculated[25].

In 3380 subjects (80.1% of the participants in this study), blood flow parameters, which included peak systolic velocity (PSV), end-diastolic velocity (EDV), and mean blood flow velocity (Vmean), were measured with the sample volume located at the center of the CCA. An insonation angle of ≤ 60° was maintained for all Doppler measurements, and RI was automatically calculated as (PSV-EDV)/PSV[26]. PI was automatically calculated as (PSV-EDV)/Vmean[27]. In the following analysis of this study, the mean values of left and right CCA measurements were used to reflect interadventitial diameter, mean IMT, RI, and PI. We estimated the reliability of the ultrasonographic measurements from 134 pairs of scans performed up to a year apart, and the estimated correlation between the scans was 0.850 for CCA interadventitial diameter, 0.854 for mean IMT, 0.698 for RI, and 0.691 for PI.

Blood Sample Measurements

The morning after an overnight fast, participants underwent the 75-g OGTT. To measure plasma glucose and serum immunoreactive insulin (IRI) levels, we drew samples just before and 30, 60, and 120 min after glucose ingestion. To measure plasma glucose, we used the hexokinase/glucose-6-phosphate dehydrogenase method for all participants. To measure serum IRI concentrations, we used a chemiluminescent immunoassay and the Beckman Coulter Unicell DXI. Insulin secretion and plasma glucose level were estimated through the total area under the insulin curve (AUCins) and the total area under the glucose curve (AUCglu) immediately after glucose ingestion and 120 min later, respectively. The trapezoidal method was used to calculate AUCins and AUCglu during the OGTT. We assessed insulin resistance according to two parameters: (1) the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated as fasting IRI (μU/ml) × fasting plasma glucose (FPG)(mg/dL)/405 [28], and (2) the Matsuda index as a measure of whole-body insulin resistance, which was calculated as 10,000 divided by the square root of FPG × fasting IRI × 2-hour postload glucose × 2-hour postload IRI[29, 30]. We also assessed insulin secretion according to two other parameters: 1) HOMA-β was estimated with the use of the homeostasis model assessment as follows: [360 × fasting IRI (μU/ml)]/[FPG (mg/dL) – 63][28]. The data of one participant who had FPG values of < 63 mg/dL (n = 1) was excluded from the analysis to avoid negative values. 2) The ratio of AUCins to AUCglu during 0 to 120 min of the OGTT (AUCins/AUCglu) was also calculated[31].

Covariate Definition and Classification of Impaired Glucose Metabolism

Participants who took antihypertensive medications, had a systolic blood pressure of ≥ 140 mmHg, or had a diastolic blood pressure of ≥ 90 mmHg were considered to have hypertension[32]. Those who took antihyperlipidemic medications had serum low-density lipoprotein cholesterol levels of ≥ 3.63 mmol/L, had serum triglyceride levels of ≥ 1.7 mmol/L, or had serum high-density lipoprotein cholesterol levels of < 1.04 mmol/L were considered to have dyslipidemia[33]. Those who took antihyperuricemic medication or had serum uric acid levels of > 0.42 mmol/L were considered to have hyperuricemia[34]. As for participants' habits, those who had a current smoking habit, regardless of the number of cigarettes smoked per day, were considered "current smokers," and those who drank ≥ 20 g of alcohol per day were "habitual drinkers." We classified the participants into five groups (NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and diabetes)

according to their glycemic status as defined by the criteria of the American Diabetes Association[35].

Statistical Analysis

Continuous variables were calculated as means ± standard deviations, and the normality of continuous variables was examined with the Kolmogorov-Smirnov test. Differences among the five groups (NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and diabetes) were analyzed with the Kruskal–Wallis test and the Steel–Dwass post hoc test was used for multiple comparison testing. Categorical variables were summarized as percentages. We used simple linear regression to evaluate the relationships between clinical characteristics, plasma glucose, serum IRI levels, and insulin resistance and insulin secretion indices, and CCA parameters. To adjust for the confounding factors, the multivariable regression models included age, sex, body mass index (BMI), smoking, drinking, estimated glomerular filtration rate, and the presence of hypertension, dyslipidemia, and hyperuricemia.

Next, to determine whether individual parameters, such as plasma glucose level, serum IRI, insulin resistance index, and insulin secretion index, were independently associated with CCA interadventitial diameter, AUCglc, AUCins, and either HOMA-IR or HOMA-β were included in the multivariable model. Similarly, AUCglu, fasting IRI level, and the Matsuda index were included in the multivariable models for RI and PI. AUCglu and HOMA-IR were included in the multivariable models for RI and PI. In each model, the inclusion of variables was determined by consideration of collinearity, which we assessed with variance inflation factors. Variables with variance inflation factors of ≥ 4.0 were excluded from the multivariable model. We considered $P<0.05$ as statistically significant. All statistical analyses were performed using the JMP 14.2 statistical software (SAS Institute, Inc., Cary, NC, USA).

Results

In total, 4218 participants (2126 men and 2092 women with a mean age of 71.5 ± 5.0 years and a mean BMI of 23.1 ± 3.1 kg/m^2) were enrolled in the present study. Participant characteristics, plasma glucose and serum insulin levels, insulin resistance and insulin secretion indices, and parameters of ultrasonographic measurements of the CCA are summarized in **Table 1**. CCA interadventitial diameter, RI, and PI were significantly higher in all participants in the isolated IFG, isolated IGT, IFG plus IGT, and diabetes groups than in those in the NFG/NGT group **(Table 2)**. The mean IMT was significantly higher in the IFG plus IGT and diabetes groups than in the NFG/NGT group.

AUCglu was significantly associated with CCA interadventitial diameter (r=0.170, $P<0.001$), mean IMT (r=0.057, $P<0.001$), RI (r=0.209, $P<0.001$), and PI (r=0.179, $P<0.001$) **(Fig. 2)**. AUCins was significantly associated with CCA interadventitial diameter (r=0.049, $P=0.002$), mean IMT (r=0.035, $P=0.022$), RI (r=0.068, $P<0.001$), and PI (r=0.063, $P<0.001$). Both HOMA-IR and the Matsuda index were significantly associated with CCA interadventitial diameter, mean IMT, RI, and PI. **Supplementary Fig. 1** shows the association of FPG, fasting and post-glucose load serum IRI levels, insulin resistance indices, and insulin secretion indices with CCA parameters in scatter plots.

After adjustment for the confounding factors, AUCglu was significantly associated with CCA interadventitial diameter (β = 0.048, $P<0.001$), RI (β = 0.144, $P<0.001$), and PI (β = 0.103, $P<0.001$) but not with mean IMT **(Table 3)**. AUCins was significantly and negatively associated with CCA interadventitial diameter ($\beta=-0.064$, $P<0.001$) but not with mean IMT. HOMA-IR was significantly associated with CCA interadventitial diameter ($\beta=-0.033$, $P=0.032$), RI ($\beta=0.054$, $P=0.002$), and PI ($\beta=0.047$, $P=0.009$) but not with mean IMT. The Matsuda index was significantly associated with RI ($\beta=-0.093$, $P<0.001$) and PI ($\beta=-0.053$, $P=0.002$). Both HOMA β ($\beta=-0.054$, $P<0.001$) and AUCins/AUCglu ($\beta=-0.072$, $P<0.001$) were significantly and negatively associated with CCA interadventitial diameter. When AUCglu, AUCins, and HOMA-IR were included together in the multivariable model for CCA interadventitial diameter, the significant association between AUCglu, and AUCins and CCA interadventitial diameter persisted. In contrast, the association between HOMA-IR and CCA interadventitial diameter was not significant **(Table 4)**. When AUCglu, fasting IRI level, and the Matsuda index were included together in the multivariable model for RI, the significant association between AUCglu and RI persisted, whereas the association of fasting IRI level and the Matsuda index with RI was not significant. When AUCglu and HOMA-IR were included together in the multivariable model for RI, the significant association between AUCglu and RI persisted, whereas the association of HOMA-IR with RI was not significant. Similar results were obtained from the analysis of PI.

Table 1. Clinical characteristics of the study participants

N	4218
Mean age, years	71.5 ± 5.0
Women, *n* (%)	2092 (50)
BMI, kg/m^2	23.1 ± 3.1
Smoking	
Never smoker, *n* (%)	2599 (62)
Current smoker, *n* (%)	387 (9)
Former smoker, *n* (%)	1232 (29)
Habitual drinker, *n* (%)	956 (23)
Hypertension, *n* (%)	1630 (39)
Dyslipidemia, *n* (%)	2702 (64)
Hyperuricemia, *n* (%)	605 (14)
eGFR, mL/min/1.73 m^2	67.6 ± 12.7
Categories of impaired glucose metabolism	
NFG/NGT, *n* (%)	1801 (43)
Isolated IFG, *n* (%)	856 (20)
Isolated IGT, *n* (%)	481 (11)
IFG plus IGT, *n* (%)	658 (16)
Diabetes, *n* (%)	422 (10)
Parameters of glucose metabolism	
Fasting PG, mmol/L	5.57 ± 0.65
AUCglu*, mmol/L·h	16.8 ± 3.8
Fasting IRI*, pmol/L	39.6 ± 24.5
AUCins†, pmol/L·h	587.1 ± 378.9
HOMA-R*	1.43 ± 0.97
Matsuda index‡	8.89 ± 6.71
HOMA-β*	56.5 ± 33.7
AUCins/AUCglu†	35.9 ± 23.4
Ultrasonographic measurements of the common carotid artery	
Diameter, mm	7.32 ± 0.77
Mean IMT, mm	0.83 ± 0.15
RI§	0.73 ± 0.06
PI§	1.61 ± 0.33

*4217 participants, †4205 participants, ‡4214 participants due to missing values.
§RI and PI were assessed in 3380 participants.
Data are expressed as mean ± standard deviation or number and percentage.
Abbreviations: AUCglu, total area under the glucose curve; AUCins, total area under the insulin curve; BMI, body mass index; eGFR, estimated glomerular filtration rate; HOMA-β, homeostatic model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima–media thickness; IRI, immunoreactive insulin; NFG, normal fasting glucose; NGT, normal glucose tolerance; PG, plasma glucose PI, pulsatility index; RI, resistance index

Discussion

In this study, we demonstrated several novel findings. First, CCA interadventitial diameter was positively associated with AUCglu during OGTT and was negatively associated with AUCins and insulin secretion indices in participants without CVD. Conversely, mean IMT was not associated with any parameters of glucose metabolism. These suggest that, in participants without CVD, the markers of arterial remodeling in CCA, not those of atherosclerosis, may reflect the effect of hyperglycemia and the resultant hyperinsulinemia. Second, both RI and PI were significantly associated with HOMA-IR and the Matsuda index, suggesting that they indicate insulin resistance development in participants without CVD.

In this study, CCA interadventitial diameter was positively associated with AUCglu, but FPG was not. CCA diameter enlargement is a focal compensating response to atherosclerosis and a part of systemic

Table 2. Ultrasonographic measurements of the common carotid artery in participants with different stages of impaired glucose metabolism

Variables	NFG/NGT	Isolated IFG	Isolated IGT	IFG plus IGT	Diabetes	*P*
Diameter, mm	7.18 ± 0.73	7.36 ± 0.80*	7.38 ± 0.79*	7.42 ± 0.76*	7.57 ± 0.79*†‡§	< .001
Mean IMT, mm	0.82 ± 0.14	0.83 ± 0.14	0.84 ± 0.15	0.84 ± 0.16‖	0.85 ± 0.15‖	0.001
RI	0.72 ± 0.06	0.74 ± 0.05*	0.74 ± 0.06*	0.74 ± 0.06*	0.75 ± 0.05*†¶	< .001
PI	1.55 ± 0.32	1.63 ± 0.32*	1.63 ± 0.35#	1.66 ± 0.35*	1.70 ± 0.33*¶**	< .001

*P < 0.001, #P < 0.005, ‖P < 0.05 versus the NFG/NGT group. †P < 0.001, **P < 0.05 versus the isolated IFG group. ‡P < 0.001, ¶P < 0.05 versus the isolated IGT group. §P < 0.001 versus the IFG plus IGT group.
Data are expressed as mean ± standard deviation.
NFG/NGT was defined as FPG of < 5.6 mmol/L and 2-h postload glucose level of < 7.8 mmol/L. IFG was defined as FPG between 5.6 and 6.9 mmol/L and 2-h postload glucose level of < 7.8 mmol/L. IGT was defined as FPG of < 5.6 mmol/L and 2-h postload glucose level between 7.8 and 11.0 mmol/L. IFG plus IGT was defined as FPG between 5.6 and 6.9 mmol/L and 2-h postload glucose level between 7.8 and 11.0 mmol/L. Diabetes was defined as FPG of ≥ 7.0 mmol/L and/or 2-h postload glucose level of ≥ 11.1 mmol/L.
Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima–media thickness; NFG, normal fasting glucose; NGT, normal glucose tolerance; PI, pulsatility index; RI, resistance index.

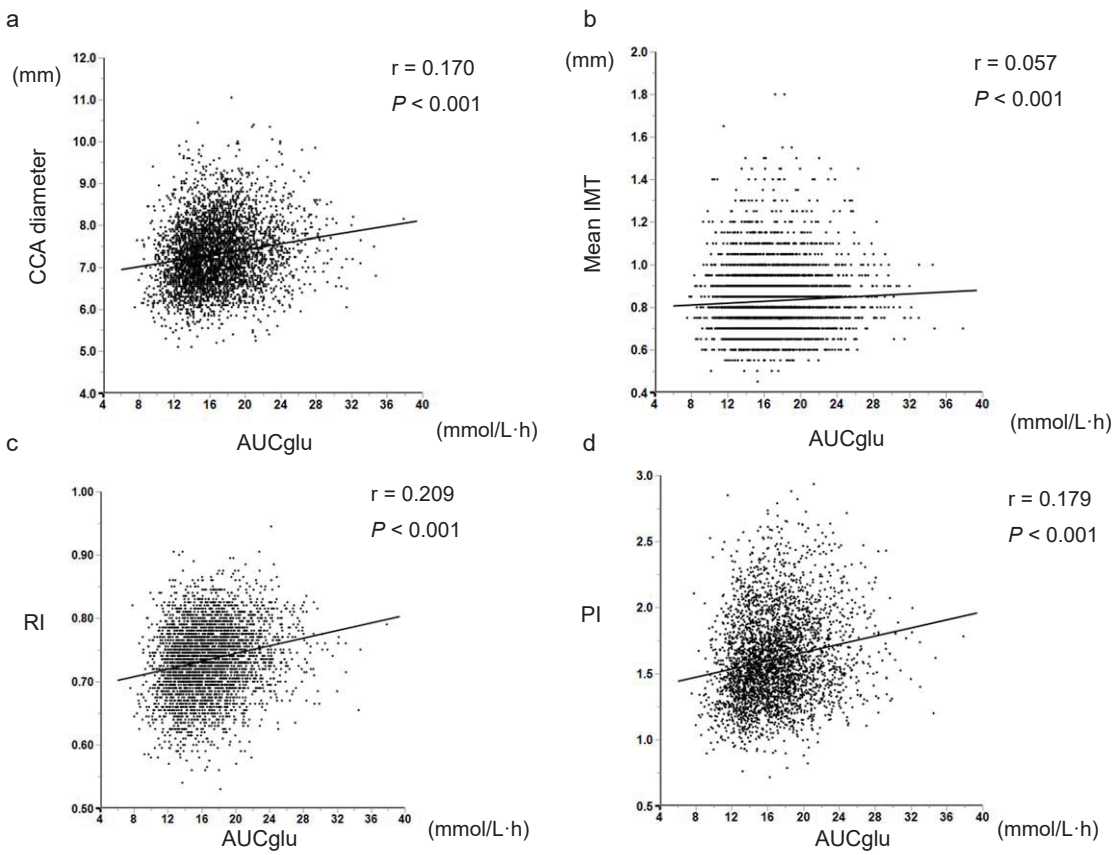

Fig. 2. Association of post-glucose-loading elevation of plasma glucose level with common carotid artery parameters.
Abbreviations: AUCglu, total area under the glucose curve; CCA, common carotid artery; IMT, intima–media thickness; PI, pulsatility index; RI, resistance index

vascular remodeling[9]. Regarding glucose metabolism, previous studies have demonstrated no significant association between CCA diameter and FPG[36, 37] and inconsistent results about the association between CCA diameter and HbA1c levels[11, 12]. However, hyperglycemia is well known to be involved in the development of arterial remodeling[38, 39]. Our results suggest that postprandial hyperglycemia may be a significant determinant for the enlargement of CCA interadventitial diameter in participants without CVD. Of interest in this study was that serum insulin level during OGTT was negatively associated with

Table 3. Association of plasma glucose and serum insulin levels, and insulin resistance and insulin secretion indices with common carotid artery measurements

	Diameter		Mean IMT		RI		PI	
Variables	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Fasting PG, mmol/L	0.026	0.061	0.011	0.483	0.080	<.001	0.061	<.001
AUCglu, mmol/L·h	0.048	<.001	0.005	0.732	0.144	<.001	0.103	<.001
Fasting IRI, pmol/L	−0.044	0.004	0.001	0.964	0.045	0.012	0.041	0.023
AUCins, pmol/L·h	−0.064	<.001	−0.018	0.259	0.029	0.084	0.018	0.276
HOMA-IR	−0.033	0.032	0.004	0.823	0.054	0.002	0.047	0.009
Matsuda index	0.017	0.255	−0.002	0.914	−0.093	<.001	−0.053	0.002
HOMA-*β*	−0.054	<.001	0.003	0.854	0.009	0.587	0.015	0.388
AUCins/AUCglu	−0.072	<.001	−0.015	0.334	−0.017	0.295	−0.015	0.373

Model included age, sex, BMI, smoking, drinking, eGFR, and the presence of hypertension, dyslipidemia, and hyperuricemia.
Abbreviations: AUCglu, total area under the glucose curve; AUCins, total area under the insulin curve; *β*, standardized partial regression coefficient; BMI, body mass index; eGFR, estimated glomerular filtration rate; HOMA-*β*, homeostatic model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immunoreactive insulin; PG, plasma glucose; PI, pulsatility index; RI, resistance index

Table 4. Multiple linear regression for diameter, resistance index, and pulsatility index

	Diameter				RI				PI			
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Variables	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
AUCglu, mmol/L·h	0.057	<.001	0.052	<.001	0.132	<.001	0.142	<.001	0.102	<.001	0.099	<.001
Fasting IRI, pmol/L					0.005	0.800			0.023	0.261		
AUCins, pmol/L·h	−0.060	<.001	−0.063	<.001								
HOMA-IR	−0.014	0.457					0.007	0.706			0.014	0.462
Matsuda index					−0.029	0.155			0.004	0.864		
HOMA-*β*			−0.008	0.673								

All models included age, sex, BMI, smoking, drinking, eGFR, and the presence of hypertension, dyslipidemia, and hyperuricemia.
Abbreviations: AUCglu, total area under the glucose curve; AUCins, total area under the insulin curve; *β*, standardized partial regression coefficient; BMI, body mass index; eGFR, estimated glomerular filtration rate; HOMA-*β*, homeostatic model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immunoreactive insulin; PI, pulsatility index; RI, resistance index

CCA interadventitial diameter after adjustment for possible confounding factors. In univariable analysis, AUCins was positively associated with CCA interadventitial diameter. This ostensible association was attributable to BMI's confounding effect because BMI was closely correlated with both AUCins and CCA interadventitial diameter (data not shown). Insulin regulates vascular homeostasis through nitric oxide, a vasodilator, and the vasoconstrictor endothelin-1 pathway[40]. The effect of hyperinsulinemia in isolation from insulin resistance on vasculature is not fully understood. However, the insulin infusion in physiological doses decreased central systolic blood pressure by decreasing wave reflection in the aorta in healthy individuals[41] and individuals with type 2 diabetes[42]. This beneficial effect of insulin on the vascular wall in the elastic arterial tree may attenuate arterial remodeling in the CCA. The inverse association between CCA interadventitial diameter and insulin secretion indices such as HOMA-*β* and AUCins/AUCglu also may support this concept. We found a contradiction concerning the association with CCA between the Matsuda index and HOMA-IR concerning insulin resistance indices. The Matsuda index is a marker of insulin resistance throughout the whole body, including skeletal muscle, which reflects plasma glucose and serum insulin levels during OGTT. Insulin resistance causes hyperglycemia and compensative hyperinsulinemia. The lack of a significant association between the Matsuda index and CCA interadventitial diameter may be attributable to differences between hyperglycemia and hyperinsulinemia. Conversely, HOMA-IR is a marker of hepatic insulin resistance, which was determined based on only FPG and fasting serum IRI levels. Higher fasting serum IRI levels seemed to have a protective effect against arterial remodeling. This may be responsible for the paradoxically inverse association between HOMA-IR

and CCA interadventitial diameter.

Wagenknecht *et al.* reported a significant association between FPG and IMT in participants with type 2 diabetes[15]. Temelkova-Kurktschiev *et al.* reported that 2-h plasma glucose level, but not FPG, was associated with IMT in participants in whom glucose metabolism was 40% impaired[16]. Kozakova *et al.* reported that insulin resistance was associated with IMT in apparently healthy middle-aged men[18]. Conversely, Larsson *et al.* reported no significant association between insulin resistance and IMT in postmenopausal women without diabetes[17]. These results may have been inconsistent because of the difference in characteristics of the study population, such as age and ethnicity and confounding factors, which had a larger effect on IMT than did impaired glucose metabolism. Two recent studies have demonstrated that the significant association between plasma glucose level and IMT was lost after adjustment for confounding factors[11, 19]. We also found that plasma glucose and serum IRI levels and insulin resistance were associated with mean IMT in univariable analysis but not after adjustment for confounding factors, including BMI and the presence of hypertension. These findings suggest that hyperglycemia per se is not a primary determinant of the development of atherosclerosis in CCA, at least in participants without CVD.

Both RI and PI have been reported as markers for the risk of stroke[43] and coronary heart disease[44]. However, little is known about the association of these CCA flow parameters with either plasma glucose level or insulin resistance. In an earlier study with a small number of participants, PI was significantly higher in participants with low levels of 1,5-anhydroglucitol than that in those with high levels of 1,5-anhydroglucitol[45] whereas another study showed no significant association between PI and either FPG or HOMA-IR[46]. In this study, we demonstrated that both RI and PI were positively associated with FPG and AUCglu. These CCA flow parameters may reflect microvascular damage evoked by hyperglycemia, in as much as RI and PI of the CCA were markers for vascular resistance distal to the measurement point[22]. Furthermore, both RI and PI were significantly associated with HOMA-IR and the Matsuda index. This may suggest that these vascular resistance indices measured at CCA reflect insulin resistance progression in participants without CVD. Insulin resistance manifests as endothelial dysfunction, including impairment of nitric oxide-dependent vasodilation, which results in vascular resistance and a decrease in microvascular blood flow. The impairment in the microvascular circulation may be responsible for insulin delivery to the target tissues and for decreased limb glucose uptake, which is the condition of insulin resistance[10]. These possible pathophysiological linkages between insulin resistance and vascular resistance may explain the findings in this study. Also, hyperglycemia may be a key intermediate pathway between insulin resistance and vascular resistance because AUCglu, but not insulin resistance indices, was significantly associated with RI and PI of the CCA when AUCglu and insulin resistance indices were included in the multivariable model.

This study had certain limitations. First, a causal relationship between CCA measurements and plasma glucose and serum insulin levels and insulin resistance may not be inferred because of its cross-sectional study design. Second, there are ethnic differences in the prevalence of obesity, the pathophysiology in diabetes[47], and CCA interadventitial diameter[48]. In this study conducted in Japan, a large proportion of participants were non-obese. This may limit the application of our findings to other ethnicities. Third, recent studies showed that type 2 diabetes or hyperglycemia was associated with IMT or atherosclerotic carotid stenosis in patients with stroke[49, 50]. Given the evidence, our results may not apply to patients with manifestations of CVD. Fourth, about 20% of our research population lacked data on RI and PI. This is mainly because RI and PI were not evaluated to save time on the carotid artery ultrasonography conducted between 2008 and 2010. The lack of RI and PI values was investigated and approved during the review of this study program by the Ethics Committee. However, we cannot exclude the possibility of selection bias due to the missing data.

Conclusions

Our study demonstrated the difference among CCA parameters with the association of plasma glucose and serum insulin levels and insulin resistance in participants without CVD. CCA interadventitial diameter was positively associated with post-glucose-loading elevation of plasma glucose level and was negatively associated with post-glucose-loading serum insulin level. Mean IMT was not associated with any parameters of glucose metabolism. Both RI and PI were associated with insulin resistance. These results may be due to the characteristics of each CCA parameters, such as a marker of arterial remodeling, atherosclerosis, or vascular resistance.

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None.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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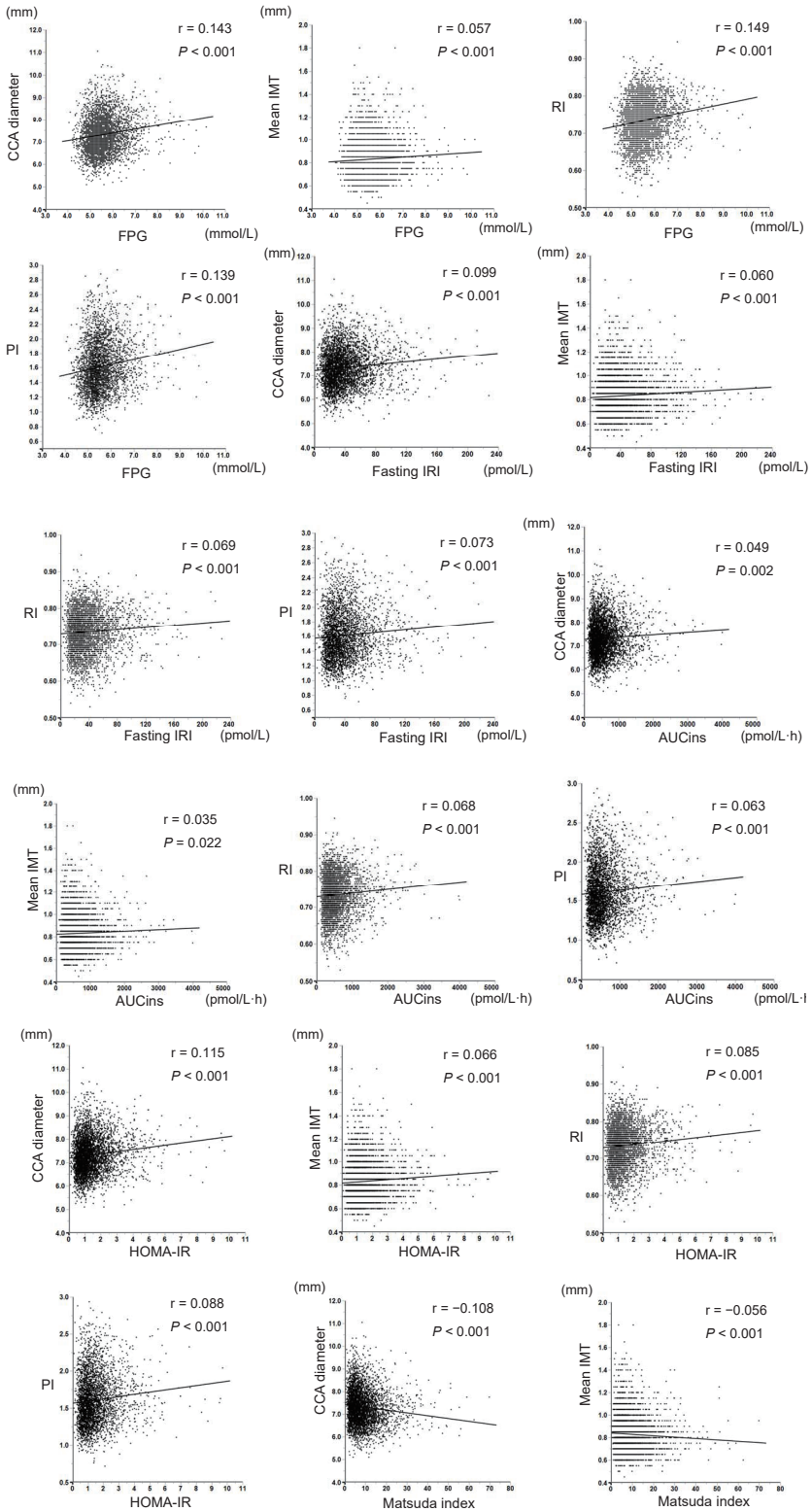
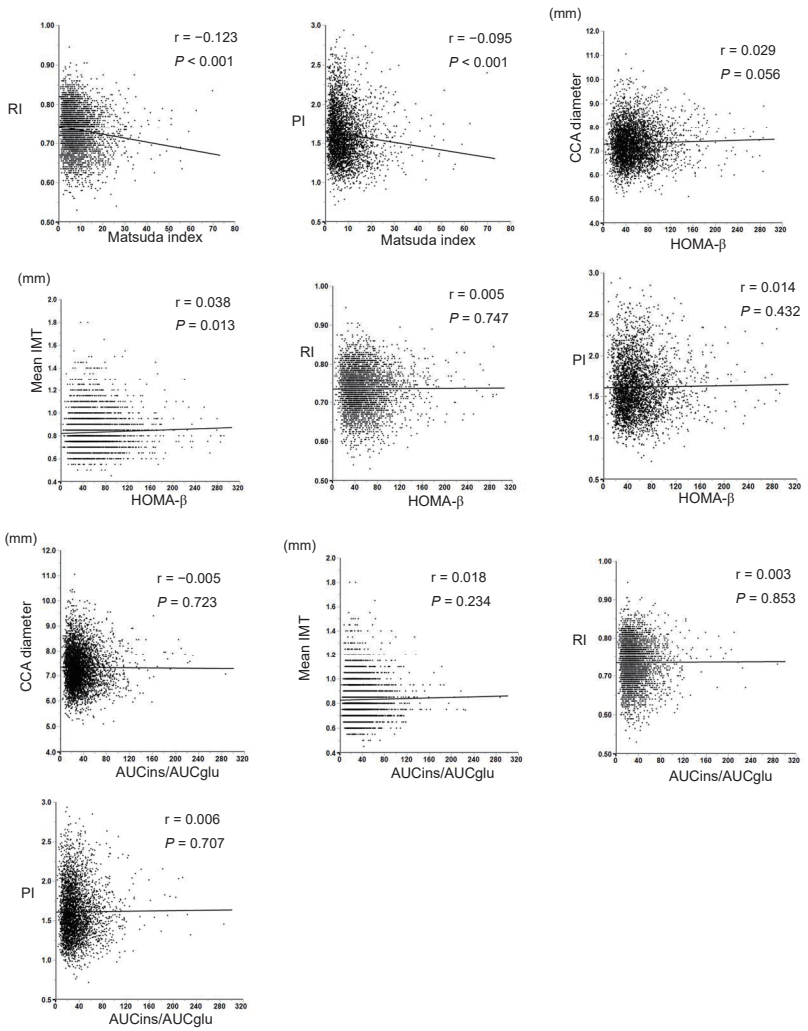


Supplementary Fig. 1. Association of the fasting plasma glucose level, fasting and post-glucose loading serum insulin levels, insulin resistance and insulin secretion indices with the common carotid artery parameters

Abbreviations: AUCglu, total area under the glucose curve; AUCins, total area under the insulin curve; CCA, common carotid artery; HOMA-β, homeostatic model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IMT, intima–media thickness; IRI, immunoreactive insulin; FPG, fasting plasma glucose; PI, pulsatility index; RI, resistance index



(Cont. Supplementary Fig. 1)