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Glycemic and blood pressure control in older patients with hypertension and diabetes: association with carotid atherosclerosis

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Abstract

Background Numerous studies have confirmed the effectiveness of slowing the progression of atherosclerosis by blood pressure (Bp) control in patients with hypertension and several studies also showed the efficacy of intensive glycemic control in decreasing progression of carotid intima-media thickness (CIMT) in patients with type 1 and type 2 diabetes. However, few studies have compared the relative importance of glycemic vs. Bp control in patients with diabetes and hypertension. We aimed to investigate the association between Bp and glycemic control and subclinical carotid atherosclerosis in older patients with hypertension and type 2 diabetes. **Methods** In a cross-sectional study, B-mode high-resolution ultrasonography of the carotid artery was performed in 670 subjects (508 males and 162 females) aged 60 years or over who had self-reported hypertension and diabetes but no history of coronary heart disease or stroke. Subjects were categorized by their systolic blood pressure: tight control, < 130 mmHg; usual control, 130–139 mmHg; or uncontrolled, ≥ 140 mmHg, and by their hemoglobin A1c (HbA1c) level: tight control, < 6.5%; usual control, 6.5%–7.5%; or uncontrolled, ≥ 7.5%, respectively. **Results** The mean CIMT was 8.20 ± 0.11 mm, and carotid plaque was found in 52.5% (352/670) subjects. Overall, 62.1% of the subjects had subclinical carotid atherosclerosis, defined as having either carotid plaque or elevated CIMT (≥ 1.1 mm). The mean CIMT was significantly different between Bp control categories (7.60 ± 0.09 mm, 7.90 ± 0.08 mm, and 8.60 ± 0.12 mm, respectively, $P = 0.03$) but not between glycemic control categories (8.20 ± 0.10 mm, 8.1 ± 0.08 mm, and 8.40 ± 0.14 mm, respectively, $P = 0.13$) using ANCOVA analysis. Multivariable logistic regression adjusting for potential confounding factors showed that usual or uncontrolled Bp control were associated with having carotid plaque (OR = 1.08 and OR = 1.42, respectively), or elevated CIMT [Odd ratio (OR) = 1.17, 95% confidence interval (CI) 1.04–2.24, and OR = 1.54, 95% CI 1.36–2.96, respectively compared to tight Bp control; but did not show glycemic control as independent predictor of either having carotid plaque or elevated CIMT. **Conclusions** In older patients with hypertension and diabetes, blood pressure control, but not glycemic control is associated with subclinical carotid atherosclerosis.

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Keywords: hypertension; diabetes; carotid intima-media thickness; carotid plaque; atherosclerosis

1 Introduction

Cardiovascular disease (CVD), principally stroke and coronary heart disease (CHD), is the leading cause of death in China^[1] and is expected to increase with further economic development and urbanization, aging of the population, and changes in diet and physical activity.^[2,3] Both hypertension and diabetes are major risk factors for CVD.^[2] The Chinese National Nutrition and Health's Survey in 2002 showed that the prevalence of hypertension in Chinese adults was 18.8% and increased by 31% compared with that in 1991,^[3,4] while

a recent study estimated the age-standardized prevalence of diabetes and prediabetes to be 9.7% and 15.5%, respectively.^[5]

Hypertension and type 2 diabetes are frequently co-existing. The prevalence of hypertension in type 2 diabetes is higher than that in the general population. At the age of 75 around 60% of patients with type 2 diabetes are hypertensive.^[6] Numerous studies have confirmed the effectiveness of slowing the progression of atherosclerosis by blood pressure (Bp) control in patients with hypertension,^[7] while several studies also showed the efficacy of intensive glycemic control in decreasing progression of intima-media thickness in patients with type 1^[8] and type 2^[9–11] diabetes. However, few studies have compared the relative importance of glycemic vs. Bp control in patients with diabetes and hypertension. We hypothesized that both Bp and glycemic control would be associated with carotid atherosclerosis in

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older patients with hypertension and type 2 diabetes who had no history of CHD or stroke.

2 Methods

2.1 Study population

In 2009, the China National Committee on Aging sponsored the program "Health Promotion Sojourn for Senior Retired Officials". From March 2009 to October 2009, a total of 15468 people aged 60 years or over who resided in Beijing had participated. Before their traveling, all participants undertook a comprehensive health examination which, in addition to a range of procedures commonly covered by a typical annual check-up in China, also included ultrasonography of the carotid artery. Among the total participants, 842 had self-reported hypertension and diabetes but no history of CHD or stroke. Of them, 678 (512 males and 156 females, mean age 68.5 years) had carotid ultrasonography examination and their data were analyzed for the present study. Information related to individual identification were removed and remained anonymous during the entire study process. The study was approved by the Institutional Review Boards of the Chinese PLA General Hospital.

2.2 Health examinations

For all participants, the health examination procedure included physical examination, a series of medical tests for blood, urine, body measurements, functional tests, and a questionnaire for lifestyle and medical history. Blood samples were drawn after a 12-h overnight fast for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose level, serum creatinine and nitrogen, and serum liver tests measurements. For all subjects with a history of diabetes, hemoglobin A1c (HbA1c) was measured. Estimated glomerular filtration rate (eGFR) was calculated using the formula from the Modification of Diet in Renal Disease Study Group.^[12] Blood pressures were measured twice with a mercury sphygmomanometer on the right upper arm with the subject seated quietly for at least 5 min and the lower value was used for analysis. Height, weight and waist circumferences (WC) were measured with the subject wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. WC was measured over the abdomen at the smallest diameter between the costal margin and iliac crest. A standardized questionnaire was used to collect information on current health status, physical activity, smoking behavior,

and physician's diagnosis of hypertension, diabetes, stroke, myocardial infarction, angina, and details of current regular medication, including antihypertensive and hypoglycemic drugs.

2.3 Carotid ultrasonography

Carotid ultrasonography was performed at 3 health examination centers designated by the China National Committee on Aging which were located in Beijing, using high-resolution B-mode ultrasound scanner (Hewlett-Packard Sonos-5500, Philips HDI 5000, Advanced Technology Laboratory, Bothell, WA; and SSA-700A Aplio, Toshiba Medical System) with 7.5-MHz to 12.5-MHz liner array transducers. To standardize the scanning procedure, all sonographers took a 2-d training course on the carotid ultrasonography protocol.^[13] With the subject in the supine position, images were obtained bilaterally from the anterior, posterior, and lateral views, with the head tilted slightly upward in the midline position. Carotid intima media thickness (CIMT) was the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, measured at the near and far walls of three 10 mm segments of distal common carotid, bifurcation (bulb), and proximal internal carotid (ICA) of both the left and right carotid arteries. For each of the 12 segments, the maximum IMT thickness at vessel wall free of atherosclerotic plaque was measured. The final CIMT was defined as the averages of maximum IMT at the 12 preselected sites. CIMT of 1.1 mm or larger was defined as elevated CIMT. Carotid atherosclerotic plaque along the defined artery segments (CCA, bulb, and ICA) of both the left and right carotid arteries was also identified and defined as a focal structure that meet any of the following 2 criteria: (1) encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value and (2) a thickness > 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.

2.4 Statistical analyses

Continuous variables are expressed as mean ± SD, and categorical variables as percentages. Student *t* test or chi-square tests were used to compare values between male and female subjects. Subjects were categorized by their systolic blood pressure: tight control, < 130 mmHg; usual control, 130–139 mmHg; or uncontrolled, ≥ 140 mmHg, and by their HbA1c level: tight control, < 6.5%; usual control, 6.5%–7.5%; or uncontrolled, ≥ 7.5%, respectively. Mean values of CIMT were compared between groups using analysis of variance (ANOVA) and then using analysis of covariance (ANCOVA). Multivariate logistic regression models were used to compute odds ratios (ORs)

and their 95% confidence interval (95% CI) of having elevated CIMT or carotid plaque. Potential confounding factors were adjusted in the ANCOVA analyses and multivariable regression models. They were age, sex, smoking, systolic blood pressure, HbA1c level, duration of hypertension, duration of diabetes, BMI, HDL-C, LDL-C, TG, and eGFR. All analyses were carried out using the Window-based SPSS statistical package (Version 16.0, SPSS Inc., Chicago, IL), and *P* values less than 0.05 were considered to be significant.

Table 1. Characteristics of male and female study subjects.

Variable	All (<i>n</i> = 670)	Male (<i>n</i> = 508)	Female (<i>n</i> = 162)	<i>P</i> *
Clinical data				
Age (yr)	68.5 ± 6.3	68.6 ± 5.9	68.3 ± 6.7	0.62
BMI (kg/m ²)	25.8 ± 2.6	26.7 ± 3.4	27.2 ± 3.8	0.11
Waist circumference (cm)	85.9 ± 7.8	86.7 ± 7.6	83.4 ± 8.2	< 0.01
Current smoker, <i>n</i> (%)	107 ± 16.0	103 ± 20	4 ± 3.2	< 0.01
Systolic BP (mmHg)	146.0 ± 21.2	146.8 ± 21.8	143.4 ± 19.6	0.08
Diastolic BP (mmHg)	82.7 ± 11.7	82.8 ± 11.8	82.2 ± 11.4	0.56
Duration of hypertension (years)	15.4 ± 6.8	16.2 ± 7.6	12.8 ± 5.2	< 0.01
Duration of diabetes (years)	10.9 ± 4.9	11.4 ± 5.4	9.6 ± 3.3	< 0.01
Current use of anti-hypertensive medication, <i>n</i> (%)	562 (83.9)	438 (86.2)	124 (76.5)	< 0.01
Current use of glucose-lowering medication, <i>n</i> (%)	368 (54.9)	266 (52.4)	102 (63.0)	0.02
Laboratory data				
Fasting glucose (mmol/L)	7.5 ± 2.0	7.5 ± 2.1	7.3 ± 1.8	0.28
HbA1c (%)	6.9 ± 1.3	6.9 ± 1.3	6.8 ± 1.3	0.39
TC (mmol/L)	5.4 ± 0.8	5.4 ± 0.8	5.3 ± 0.9	0.18
HDL-C (mmol/L)	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.00
LDL-C (mmol/L)	3.2 ± 0.7	3.2 ± 0.7	3.3 ± 0.7	0.11
Triglycerides (mmol/L)	1.9 ± 1.1	1.9 ± 1.1	1.8 ± 1.0	0.30
eGFR, mL/min per 1.73 m ²	82.9 ± 18	82.8 ± 17	83.2 ± 18	0.80
Carotid ultrasonographic data				
Carotid plaque, <i>n</i> (%)	352 (52.5)	268 (52.8)	84 (51.9)	0.86
Elevated CIMT, <i>n</i> (%)	125 (18.7)	104 (20.5)	21 (13.0)	0.037
Either carotid plaque or elevated CIMT, <i>n</i> (%)	416 (62.1)	313 (61.6)	103 (63.6)	0.71
Mean CIMT (mm)	8.2 ± 0.11	8.2 ± 0.11	8.1 ± 0.11	< 0.01
Blood pressure control				
Tight, <i>n</i> (%)	146 (21.8)	103 (20.3)	43 (26.5)	0.042
Usual, <i>n</i> (%)	207 (30.9)	151 (29.7)	56 (34.6)	
Uncontrolled, <i>n</i> (%)	317 (47.3)	254 (50.0)	63 (38.9)	
Glucose control				
Tight, <i>n</i> (%)	134 (20.0)	97 (19.1)	37 (22.8)	0.49
Usual, <i>n</i> (%)	338 (50.4)	262 (51.6)	76 (46.9)	
Uncontrolled, <i>n</i> (%)	198 (29.6)	149 (29.3)	49 (30.2)	

Values are presented as mean ± SD. *Compared between male and female subjects using Student *t* test or chi-square test. BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; CIMT: carotid intima media thickness.

3 Results

3.1 Characteristics of the study subjects

Characteristics of the study subjects were showed in Table 1. Of all 678 subjects, six were excluded because of missing information on laboratory measures of interest (HbA1c and TC or HDL-C) and two were excluded because of missing information on blood pressure, leaving 670 participants for analysis. There were 508 males and 162 females. The mean age was 68.5 ± 6.3 years. There were no

significant differences between male and female subjects in cardiovascular risk factor levels except that the male subjects had longer duration of hypertension and diabetes, greater waist circumference and more frequently were current smoker. The mean CIMT was 8.20 ± 0.11 mm, and carotid plaque was found in 52.5% (352/670) subjects. Overall, 62.1% of the subjects had subclinical carotid atherosclerosis, defined as having either carotid plaque or elevated CIMT, or both. Compared to female subjects, the males were more often to have elevated CIMT and had greater mean CIMT level. Of all subject, 47.3% had uncontrolled blood pressure and 29.6% had uncontrolled glycemia. Bp control was poorer in male subjects, but there was no gender difference in terms of glycemic control.

3.2 Blood pressure control and subclinical carotid atherosclerosis

Of all study subjects, 21.8% were observed to have tight control; 30.9%, usual control; and 34%, uncontrolled systolic BP (Table 1). As showed in Table 2, with improved Bp control, there were decreases in both the prevalence of carotid plaque and the prevalence of elevated CIMT. The

mean CIMT increased with poorer Bp control and the difference remained significant after adjustment for other confounding factors by using ANCOVA analysis. Multivariable logistic regression showed that compared to subjects with tight Bp control, subjects with usual or uncontrolled blood pressure had greater risk for having carotid plaque (OR = 1.08 and OR = 1.42, respectively), or having elevated CIMT(OR = 1.17 and OR = 1.54, respectively). (Table 3).

3.3 Glycemic control and subclinical carotid atherosclerosis

The rates of subjects with tight, usual, and uncontrolled HbA1c were 20%, 50.4% and 29.6%, respectively (Table 1). Of the 198 glycemic uncontrolled subjects, the mean HbA1c level was $8.6 \pm 1.8\%$. The mean CIMT in glycemic tight, usual, and uncontrolled group were 8.2 mm, 8.1 mm and 8.4 mm, respectively ($P = 0.02$ by ANOVA). The prevalence of carotid plaque and elevated CIMT in subjects of glycemic uncontrolled group were 61.1% and 24.7%, respectively, which were significantly higher than those of subjects of tight or usual control group, with chi-square tests.

Table 2. Carotid ultrasonography results by different blood pressure and glycemic control categories.

Variable	Blood pressure control			<i>P</i>	Glycemic control			<i>P</i>
	Tight (n = 146)	Usual (n = 207)	Uncontrolled (n = 317)		Tight (n = 134)	Usual (n = 338)	Uncontrolled (n = 198)	
Carotid plaque, n (%)	58 (39.7)	93 (44.9)	201 (63.4)	< 0.01	65 (48.5)	166 (49.1)	121 (61.1)	0.02
Elevated CIMT, n (%)	19 (13.0)	32 (15.5)	74 (23.3)	0.015	22 (16.4)	54 (16.0)	49 (24.7)	0.03
CIMT (mm)	7.6 ± 0.09	7.9 ± 0.08	8.6 ± 0.12	0.03*	8.2 ± 0.10	8.1 ± 0.08	8.4 ± 0.14	0.13*

Values are presented as mean \pm SD. *Obtained by analysis of covariance, adjusted for age, sex, smoking, duration of hypertension, duration of diabetes, body mass index, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, estimated glomerular filtration rate, and hemoglobin A1c (for blood pressure category) or systolic blood pressure (for glycemic control category).

Table 3. Adjusted ORs of having elevated CIMT or carotid plaque by blood pressure and glycemic control categories.

Category	Elevated CIMT			Carotid plaque		
	OR*	95%CI	<i>P</i>	OR*	95%CI	<i>P</i>
Blood pressure control						
Tight		Reference			Reference	
Usual	1.17	1.04–2.24	0.03	1.08	1.02–1.34	0.04
Uncontrolled	1.54	1.36–2.96	< 0.01	1.42	1.14–1.98	< 0.01
Glycemic control						
Tight		Reference			Reference	
Usual	0.96	0.44–2.24	0.21	1.02	0.54–2.06	0.11
Uncontrolled	1.13	0.58–3.42	0.08	1.16	0.68–3.72	0.07

*Obtained by logistic regression, adjusted for age, sex, smoking, duration of hypertension, duration of diabetes, body mass index, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, estimated glomerular filtration rate, and hemoglobin A1c (for blood pressure category) or systolic blood pressure (for glycemic control category). OR: odds ratio; CI: confidence interval.

However, multivariable logistic regression analyses, after adjustment for confounding factors failed to show glycemic control as independent predictor of either carotid plaque or elevated CIMT. Similarly, the significance of differences of the mean CIMT among glycemic control groups was attenuated when using ANCOVA and adjusted for confounding factors ($P = 0.13$) (Table 1 and Table 2).

4 Discussion

In this cross-sectional study of elderly subjects with diabetes and hypertension who had no history of CHD or stroke, we investigated the independent association of Bp control and glycemic control with CIMT and the presence of carotid plaque. We found that in these patients, subclinical carotid atherosclerosis was quite common (observed in 62.1% of the subjects), which is in consistent with previous studies; But more importantly, we found that in these patients, Bp control but not glycemic control was associated with subclinical carotid atherosclerosis. The latter finding was somewhat unexpected and we will focus our discussion on this result.

4.1 Interpretation of findings

Hypertension is a major risk factor for carotid intima-media thickening and for carotid plaque.^[7,14,15] Numerous studies have confirmed that antihypertensive can slow the progression of atherosclerosis in patients with^[14] or without^[7] diabetes. Therefore, our finding that Bp control was associated with subclinical carotid atherosclerosis is in consistent with previous reports.

Several studies have also documented the relationship between blood glucose^[16] or HbA1c^[11] level and CIMT in hypertensive patients with diabetes. In the present study of elderly subjects, however, we did not observe an independent association between glycemic control and carotid atherosclerosis after adjustment for carefully selected confounding factors, including the duration of disease. There are several possible reasons for this finding of ours. First, compared to those in patients with hypertension, there have been much fewer studies of the relationship between glycemic control and atherosclerosis in individuals with type 2 diabetes, and whether A1C is independently associated with the progression of atherosclerosis remains controversial.^[11] Although diabetes significantly increases the risk of cardiovascular events, the relative increase in events for each percent increase in glycated hemoglobin is modest.^[17] The UKPDS implied that in hypertensive patients with type 2 diabetes, Bp control is more beneficial than glycemic control for reduction of all end points,

particularly of macrovascular disease.^[18] More recently, both ACCORD^[19] and ADVANCE^[20] trials showed that near-normal glycemic control for a median of 3.5 to 5 years does not reduce cardiovascular events within that time frame. Therefore, if there do exist a relationship between glycemic control and carotid atherosclerosis, it might be too weak to be observed by a study with relatively small sample size like our present study; Second, there might be a change with age for the association between glycemic control and atherosclerosis. In an analysis of participants aged 45 to 64 years in the Atherosclerosis Risk in Communities (ARIC) study and among participants 65 years and older in the Cardiovascular Health Study (CHS), Howard *et al.*^[21] found that although most risk factors continue to be associated with increased atherosclerosis at older ages, there was a significantly smaller impact of diabetes among older age strata; Third, it has been reported that several anti-hypertensive drugs, including thiazide diuretics and beta-blockers, might increase blood glucose level,^[22] this diabetogenic effects of antihypertensive drugs, may tend to attenuate the association between HbA1c and atherosclerosis. The majority of our study subjects were taking antihypertensive drugs, while only half of them were taking hypoglycemic medications, suggesting the possible interaction of antihypertensive drugs and HbA1c in our study. However, we did not collect data on specific antihypertensive medication, because we found self reports on the name of using drugs was impossible or unreliable for elderly people, therefore, the hypothesis that antihypertensive medication use may weaken the association between HbA1c level and atherosclerosis remains to be assumptive.

4.2 Study limitations

There were several limitations of our study. First, as mentioned above, the relatively small size of study population might not powerful enough to detect a weak association; second, we relied exclusively on self-reported information on the diagnosis, duration and medication use of diabetes and hypertension, which might be subject to memory errors, especially in older people; third, all study subjects were retired officials with high socioeconomic status who had much better health care service compared to general population of China, as reflected in the high level of both Bp and glycemic control, and the relatively low HbA1c level even in glycemic uncontrolled group, which may limit the generalizability or external validity of our conclusion.

4.3 Clinical implications

Our study provided an implication for the management of elderly patients with both hypertension and diabetes,

particularly in population with limited health care resource. From the clinical point of view, both glycemic and Bp control are important and effective in reducing macrovascular and microvascular complications in patients with hypertension and diabetes.^[23] However, in the real world, due to factors such as poor access to regular medical care, affordable health insurance, poor social support, limited health literacy, and poor patient-clinician communication, the rate of adequate control for Bp in patients with hypertension^[24] or for glucose in patients with diabetes^[25] remain disappointingly low, especially in developing countries such as China, where healthcare resources are limited. Clinicians often have to consider a priority among the multiple therapeutic goals in the management of patient with diabetes and hypertension. In addition, for diabetes patients, especially the elderly patients, the complexity of treatment regimens for comorbidities may limit their self-efficacy. Our study provides supportive data on relaxed glycemic goals in older adults^[23] and suggests that from the view point of preventing macrovascular complication, Bp control might be prior to glycemic control in hypertensive diabetics.

4.4 Conclusions

In conclusion, we found that in elderly subjects with diabetes and hypertension who had no history of CHD or stroke, subclinical carotid atherosclerosis was quite common and in these patients, Bp control but not glycemic control was associated with subclinical carotid atherosclerosis. Our study provides supportive data on relaxed glycemic goals in older adults and suggests that from the view point of preventing macrovascular complication, Bp control might be prior to glycemic control in hypertensive diabetics. However, because of the cross-sectional nature of our study, whether these findings have implications for the long-term prevention of cardiovascular complications remain to be proven.

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