The Relationship between the Breast Arterial Calcification Detected by Mammography and the Hypertensive Retinopathy in Hypertensive Women

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Objective: The purpose of this study was to investigate the relationship between the breast arterial calcification (BAC) detected by mammograms and the hypertensive retinopathy (HR) in hypertensive women who underwent ophthalmologic examination.

Materials and Methods: Screening mammography was performed in 99 hypertensive women and these women also underwent an ophthalmologic examination. The presence of arterial calcification and the number of calcified blood vessels in each breast were evaluated. The grade of HR was determined. The presence of BAC and the number of blood vessels involved was compared according to the presence of HR and the grade of HR.

Results: Among the 99 patients, HR was detected in 70 patients, and of these 70 patients, 42 patients had grade I HR and 28 had grade II HR. BAC was detected in 54 cases. Forty-six patients with HR (66%) and eight patients without HR (27%) were diagnosed with BAC after they underwent mammographic examination. The prevalence of BAC in the subjects who had HR was statistically higher than that in those subjects who did not have HR ($p < 0.01$). The grade of HR was not significantly associated with BAC ($p > 0.05$). The positive predictive value of the BAC detected on mammography for HR was 0.80 in those subjects who were $\geq$ 60 years old.

Conclusion: The detection of BAC by mammography is associated with an increased risk of HR, and particularly for patients after the age of 60. The findings of BAC may be related to hypertensive end-organ damage, and performing mammograms might contribute to predicting the presence of ophthalmologic hypertensive complications in these patients.

Hypertension has profound effects on the structure and function of the eye (1). The retinal circulation undergoes a series of pathophysiological changes in response to elevated blood pressure. These changes are clinically displayed as a spectrum of signs that are commonly referred to as hypertensive retinopathy (HR) (2, 3). The signs of HR are frequently seen in adults 40 years and older, and they are predictive of the incident of stroke, cerebral atrophy, a reduced cognitive performance and congestive heart failure and the cardiovascular mortality (1, 4).

Breast arterial calcifications (BACs) are common findings on screening mammography. The prevalence of BAC increases with increasing age and this is observed in 9 – 12% of women older than 50 years (5, 6). BAC is classified as medial arterial calcification, which is different from intimal calcification (7). Several studies have found BAC to be associated with cardiovascular disease, diabetes or hypertension, but few of

these studies have discussed the association of BAC with hypertension (6, 8 −11). Further, none have investigated the association of BAC with the systemic vascular complications of hypertension such as HR. In this study, we investigated the relationship between the BAC detected on mammograms and HR in hypertensive women who underwent an ophthalmologic examination.

MATERIALS AND METHODS

The study protocol was approved by our local ethics committee. From September 2006 to April 2007, 346 consecutive hypertensive women older than 18 years and who underwent an ophthalmologic examination at our hospital were asked to participate in this study. Of these, 99 hypertensive women gave their informed consent to be included in the study. The duration of the hypertension ranged from one month to 25 years (mean duration: 6.1 ± 3.8 years).

Direct and indirect ophthalmoscopy was performed by a single, experienced ophthalmologist on all the patients after pupil dilatation. The grade of HR was determined according to the Keith-Wagener classification (12). This classification typically consists of four grades of hypertensive retinopathy with increasing severity: grade 1 consists of mild generalized retinal arteriolar narrowing; grade 2 consists of more severe narrowing of the retinal arterioles and arteriovenous nicking is also seen; grade 3 consists of the grade 1 and 2 signs plus the presence retinal hemorrhages or exudates; grade 4 consists of the signs in the preceding three grades plus optic nerve edema and macular exudates.

Each participant filled out a personal history form with details regarding their lactation period, parity, the use of oral contraceptives and other hormonal drugs, their menopausal status and the presence or absence of chronic illnesses such as hypertension or diabetes. Mammography was performed within two weeks of the ophthalmologic examination with using a Mammomat 3000® (Siemens, Sweden, TA) mammography unit. The mediolateral oblique and craniocaudal projections were obtained for both screening and diagnostic purposes, and they were evaluated by an experienced radiologist (who was kept "blind" to the clinical features of the patient), and according to the breast reporting system recommended by the American College of Radiology (13). The presence of arterial calcification and the number of calcified blood vessels in each breast were recorded. BAC was characterized by the presence of linear calcium deposits along the periphery of the tapered structures whose configuration was typical of arteries, and this was distinct from breast ducts.

The presence of BAC and the number of blood vessels involved was compared with the presence of HR and the grade of HR. Statistical analysis was performed using SPSS 15.0 for Windows® (SPSS, Inc., Chicago, IL). Mann-Whitney tests, Fisher's exact tests and Yates' corrected chi-square (continuity correction) tests were all used in the evaluation. The results were considered statistically significant at p values < 0.05.

RESULTS

Of the 346 hypertensive women who underwent fundoscopic examination during the study period, 99 (mean age: 57 years, age range: 41 −75 years) consented to be included in the study. HR was detected in 70 patients (71%), and of these, 42 (60%) had grade I and 28 (40%) had grade II HR (Tables 1, 2).

Breast arterial calcification was detected in 54 (54.5%) cases; BAC was detected in one breast in 26 (48.1%) cases and in both breasts in 28 (51.9%) cases. For the patients with BAC, 22 (40.8%) had calcifications in a single blood vessel, 18 (33.3%) had calcifications in two blood vessels and 14 (25.9%) had calcifications in more than two blood vessels. Forty-six patients with HR (66%) and eight patients without HR (27%) were diagnosed with BAC on mammography (Table 1). The sensitivity of the BAC detected on mammography for determining the presence of HR was 85%. No patient had mammographic findings that were suggestive of malignancy.

The ages and the duration of hypertension of the patients who were diagnosed with BAC (mean age: 57.5 ± 8.3 years, age range: 41 −71 years) were similar to those patients without BAC (mean age: 54.8 ± 7.6 years, age range: 43 to 71 years). The average duration of hypertension for the subjects who had BAC was 5.0 ± 3.4 years,

Table 1. Relationship between BAC and HR

	BAC (+) (n = 54)	BAC (−) (n = 45)
HR (+) (n = 70)	46	24
HR (−) (n = 29)	8	21

Note.—BAC = breast arterial calcification, HR = hypertensive retinopathy

Table 2. Relationship between BAC and Grades of HR

	BAC (+) (n = 54)	BAC (−) (n = 45)
Presence of HR	46 (70)	24 (29)
Grade I HR	26	16
Grade II HR	20	8

Note.—BAC = breast arterial calcification, HR = hypertensive retinopathy

but this was 7.0 $\pm$ 3.8 years for the subjects without BAC (Table 3).

The incidence of BAC for the patients who had HR (66%) was significantly higher than that for those patients who did not have HR (27%) ($p < 0.01$). The ages of the patients with HR and who were diagnosed with BAC ranged from 41 to 71 years (mean age: 58.4 $\pm$ 8.9 years). The ages of the patients without HR and who were diagnosed with BAC ranged from 50 to 57 years (mean age: 53.5 $\pm$ 2.8 years). The age-specific incidence of BAC for the subjects with or without HR is given in Table 4. As

listed in Table 4, the prevalence of BAC between the two groups showed a statistically significant difference for the subjects older than 60 years. The average duration of the hypertension in the patients with HR and who were diagnosed with BAC was 4.8 $\pm$ 3.5 years, but this was 4.0 $\pm$ 1.1 years for the patients without HR and who were diagnosed with BAC.

The duration-specific prevalence of BAC for the patients with or without HR is given in Table 5. As listed in Table 5, there was a statistically significant difference in the prevalence of BAC for the patients with HR and who had the disease for more than five years. No significant association between the grade of HR and BAC was found statistically ($p > 0.05$) (Table 2). In addition, no relationship was detected between the extent of the vessel involvement of BAC and the presence of HR ($p > 0.05$) (Table 6). However, when the cases were stratified by the extent of the vessel involvement of BAC and the grade of HR, the patients with multivessel BAC had higher grades of retinopathy (Table 7).

Table 3. Distribution of Patients' Ages and Duration of Hypertension of Hypertensive Patients according to Presence of BAC

	BAC (+) (n = 54)	BAC (−) (n = 45)
Age (years)	57.5 $\pm$ 8.3	54.8 $\pm$ 7.6
Duration of hypertension (years)	5.0 $\pm$ 3.4	7.0 $\pm$ 3.8

Note.— BAC = breast arterial calcification

Table 4. Age-Specific Prevalence of BAC in Hypertensive Patients with or without HR

	HR +		HR −		p value
	BAC (+)	BAC (−)	BAC (+)	BAC (−)	
< 60 years	22 (55)	18 (45)	8 (35)	15 (65)	> 0.05
> 60 years	24 (80)	6 (20)	0 (0)	6 (100)	< 0.001
Total	46 (66)	24 (34)	8 (28)	21 (72)	< 0.01

Note.— Numbers in parentheses are percentages. BAC = breast arterial calcification, HR = hypertensive retinopathy

Table 5. Duration-Specific Prevalence of BAC in Hypertensive Patients with or without HR

	HR +		HR −		p value
	BAC (+)	BAC (−)	BAC (+)	BAC (−)	
< 5 years	18 (75)	6 (25)	4 (40)	6 (60)	> 0.05
> 5 years	28 (61)	18 (39)	4 (21)	15 (79)	< 0.01
Total	46 (66)	24 (34)	8 (28)	21 (72)	< 0.01

Note.— Numbers in parentheses are percentages. BAC = breast arterial calcification, HR = hypertensive retinopathy

Table 6. Relationship between Presence of HR and Extent of BAC Vessel Involvement

	HR (+) (n = 70)	HR (−) (n = 29)
Presence of BAC	46 (54)	8 (45)
Single-vessel involvement	20	2
Two vessels involvement	14	4
Multi-vessel involvement	12	2

Note.— BAC = breast arterial calcification, HR = hypertensive retinopathy

Table 7. Relationship between Grades of HR and Extent of BAC Vessel Involvement

	HR (+) (n = 70)	
	Grade I	Grade II
Presence of BAC	26 (54)	20 (54)
One or two vessel involvement	22	12
Multi-vessel involvement	4	8

Note.— BAC = breast arterial calcification, HR = hypertensive retinopathy

DISCUSSION

Arterial calcifications are commonly revealed on mammography, and these lesions are caused by extensive deposition of calcium in the media layer of the peripheral arterioles. This condition is called Monckeberg medial calcific sclerosis or medial arterial calcification. Monckeberg medial calcific sclerosis is different from intimal calcification, and its exact pathogenesis is still not known (14 −17). Although medial arterial calcification is presumed to be the result of the aging process, it may also be an indicator of diabetes mellitus (DM), hypertension and other vascular diseases (14 −17). Baum et al. (17) have proposed that the BAC detected on mammography might predict clinically undiagnosed cases of DM, 17 and other studies have proposed that the mammogram findings may enable prediction of diabetic complications and the earlier detection of systemic vascular damage (10, 15, 18). Even though many studies have reported on the association of BAC with diabetes and the cardiovascular risk, none have focused on the association of BAC with the systemic vascular complications of hypertension such as HR.

BAC is considered to be an independent risk factor for coronary artery disease in older age patients, and especially for the women with DM; the cardiovascular mortality is found to be 40% higher among the patients with BAC (8, 10, 15). Markopoulos et al. (19) showed that there is a correlation between BAC, as detected by mammography, and systemic vascular diseases; they claimed that BAC is a reliable indicator of systemic vascular atherosclerosis (19). Medial arterial calcification has been found to be predictive of diabetic complications and mortality (18). A recent study that examined the association between BAC and cardiovascular disease risk factors suggested that there is a strong relationship between BAC and coronary artery disease (20). The underlying mechanism of BAC, which is a form of medial arterial calcification, and its relation with cardiovascular disease is not well understood (7). However, Kemmeren et al. (10) studied the relationship of medial arterial calcification with cardiovascular mortality, and they found that it could be explained by the concomitant presence of intimal disease.

Hypertensive retinopathy refers to the retinal microvascular signs that are related to increased blood pressure; HR is also regarded as a marker of systemic vascular disease that occurs elsewhere in the body (1). Population-based studies that used standardized assessment methods to determine the signs of retinopathy have detected signs of HR in 2 −14% of the nondiabetic population that's aged 40 years and older (21, 22). The relationship between HR and stroke has been the most consistent, and this has been supported by the previous anatomical, physiological, and pathological studies (3, 23). Some investigators have proposed that moderate HR could portend congestive heart failure. HR is also associated with the presence of end-organ damage such as left ventricular hypertrophy and renal impairment (24, 25). Some investigators have suggested that any patient with hypertension should undergo ophthalmological assessment to detect HR (1).

In this series, we found a higher prevalence of BAC in the subjects with HR than in those subjects without HR ($p < 0.01$). Thus, BAC was strongly correlated with HR in the hypertensive patients of our study. The duration of the disease was not correlated with BAC in the hypertensive patients. However, the frequency of BAC showed a significant difference between the HR positive and HR negative patients with an increase of the duration of hypertension. In addition, the prevalence of BAC in the subjects with HR and who were 60 years or older was significantly higher than that in those subjects without HR ($p < 0.001$). These results show that advancing age is one of the factors related to BAC in the hypertensive patients with HR. HR was approximately 1.6-fold more common in the subjects with BAC than in those subjects without BAC, but the duration of hypertension in the subjects with or without BAC was 5.0 $\pm$ 3.4 and 7.0 $\pm$ 3.8 years, respectively ($p > 0.05$).

In this study, the patients with multivessel BAC had higher grades of retinopathy, but the relationship between the extent of vessel involvement and the grades of retinopathy was not statistically significant ($p > 0.05$).

This study has several limitations. One of the limitations is that the study concentrated on patients who were suspected to have HR and who underwent ophthalmological examination, so this sample is not characteristic of the general population. In addition, our sample size was small. Thus, this study's results need to be corroborated and reaffirmed by a conducting another similar study with a larger sample size. Another limitation of this study is that the patients were not assessed in terms of the risk factors of HR (e.g., the total cholesterol, HDL cholesterol, fasting glucose and serum creatinine levels and the body mass index). Therefore, the difference between the hypertensive patients with or without BAC in terms of specific HR risk factors could not be evaluated in this study.

Hypertensive changes in the breast vessels may be paralleled by those in the retina, and the presence of BAC on mammography was associated with an increased risk of hypertensive retinopathy, and especially in women older than 60 years. It is possible that HR indicates the duration

and severity of hypertension, which affects the risk of suffering cardiovascular events. Consequently, BAC may be related to hypertensive end-organ damage, and so performing mammograms may contribute to the earlier detection of hypertensive complications and vascular damage.

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