

Original

# Serum MMP-9 in Females Have Higher Correlation with DWI-Positive Findings for Carotid Artery Stenting than in Males

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## Summary

**Introduction:** Embolus due to plaque rupture is a risk of cerebral infarction for carotid artery stenting (CAS). Female have been controversial as a risk factor for cardiovascular interventions in recent years. MMP-9 has been previously reported to be associated with acute ischemic stroke and to be a potential marker for arteriosclerosis.

Therefore, this paper aimed to investigate the gender difference of embolic complications for CAS using MMP-9.

**Material and Methods:** We analyzed 46 consecutive cases of CAS performed with distal balloon protection, including 34 males and 12 females. Serum levels of matrix metalloproteinase (MMP)-9 were measured before and after CAS. Embolic events were examined in Diffusion Weighted Imaging (DWI) on MRI the next day after CAS.

**Results:** 13 cases (28.3%) had DWI-positive findings after CAS, and these results showed a significant gender difference (female 58.3% vs. male 17.6%,  $p < 0.05$ ). Pre-CAS MMP-9 was significantly higher in females than in males (661.7 vs. 428.1 ng/ml,  $p < 0.05$ ).

Pre-CAS MMP-9 tended to be higher in DWI-positive cases than DWI-negative cases with no significant difference (676.9 vs. 415.0 ng/ml,  $p = 0.051$ ).

**Conclusion:** High serum MMP-9 in female have correlation with DWI positive findings after CAS. We suggest that high serum MMP-9 have a risk of cerebral infarction for CAS. Considering the results, CAS should be carefully performed, especially in female.

**Key Words:** MMP-9, DWI-positive findings, female, CAS

## Introduction

Several large studies have shown the efficacy of ca-

rotid stenting (CAS) for carotid artery stenosis in the neck<sup>1)</sup>. Protective devices are useful for reduction of distal embolic complications in CAS<sup>2)</sup>, however, CAS

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has constantly risks associated cerebral embolism<sup>3</sup>. Arteriosclerotic plaque may cause inflammatory changes, and biomarkers such as matrix metalloproteinases (MMPs) have been described<sup>4,5</sup>. Among these MMPs, we have focused on MMP-9<sup>6,7</sup>. Several studies<sup>13,15,17,18,21,25</sup> have shown poorer results in female patients after cardiovascular interventions, for reasons that are unknown. In this study, we analyzed a gender difference related to embolic events, serum MMP-9 in patients before and after CAS.

## Patients and Methods

The subjects were 46 consecutive patients with carotid artery stenosis treated with CAS using distal balloon protection. In our general use of CAS, distal balloon protection, distal filter protection or the flow reversal method is selected based on the characteristics of each case, including the plaque volume, collateral blood flow, and access route. To compare each data under the same condition, we selected Carotid Guard-wire™ (Medtronic, Minneapolis, MN, USA)<sup>8</sup> for the distal balloon protection system and WALLSTENT™ (Boston Scientific, Marlborough, MA, USA) for the self-expanding closed cell stent in this study. CAS was indicated for patients with > 50% symptomatic stenosis and > 80% asymptomatic stenosis.

All operators were experienced senior staff with a Japanese neurointerventional license.

Informed consent was obtained from all patients for use of data in this study.

The qualitative evaluation of plaque before CAS was evaluated by MRI images using Black Blood (BB) method. All patients took dual anti-platelet therapy (DAPT) one or two week before CAS.

The procedure was performed under local anesthesia and intravenous injection of 5000 units of heparin. In all 46 cases, we used a 8 Fr guiding catheter to the common carotid artery from the femoral artery. During the CAS procedure, 5 ml of blood was collected from a sheath in the femoral artery before inserting the guiding catheter and another 5 ml of blood from an aspiration catheter in the carotid artery just before deflation of the distal balloon after stenting. The first sample was collected pre-CAS and the second sample post-CAS. MMP-9 was measured by a one-step sandwich enzyme immunoassay (EIA) using two monoclo-

nal antibodies (Kyowa Pharma Chemical Co., Ltd). Normal ranges using this assay are  $38 \pm 15$  ng/ml for MMP-9<sup>9</sup>.

The presence of cerebral infarction by DWI on MRI was evaluated the next day after CAS. DWI-positive findings were defined based on the presence of a new small single spot in the brain.

The association and gender differences between MMP-9 and DWI findings were examined using non-parametric statistical method.

We were approved by the Institutional Review Board of Dokkyo Medical University in method (approval number; 1814).

## Results

Baseline characteristics had no significant difference between males and females (Table 1).

All 46 procedures were performed successfully without adverse events. 13 cases had positive findings in DWI on the day after treatment (28.3%), with a significantly higher rate in females than in males (7/12 (58.3%) vs. 6/34 (17.6%),  $p < 0.05$ , Table 2). Pre-CAS MMP-9 tended to be higher in DWI-positive cases than DWI-negative cases with no significant difference (676.9 vs. 415.0 ng/ml,  $p = 0.051$ , Table 2), however, Pre-CAS MMP-9 was significantly higher in females than in males (661.7 vs. 428.1 ng/ml,  $p < 0.05$ , Table 3). Female patients had higher pre-CAS MMP-9 and a higher rate of DWI-positive findings than males ( $p < 0.05$ , Table 3) and DWI-positive cases in females had higher Pre-CAS MMP-9 than DWI-positive cases in males with a statistically significant difference (812.9 vs. 518.3 ng/ml,  $p < 0.05$ , Table 4).

Black-Blood (BB) T1 high intensity area of carotid plaque on MRI and Post-CAS MMP-9 had no relationship with DWI findings (Table 2).

## Discussion

Embolic complications for interventional radiology (IVR) include age, operator experience, inflammation, and arteriosclerosis<sup>10-12</sup> and female gender is also a risk factor for surgical treatment of carotid artery lesions<sup>13,21</sup>. The causes for the poorer outcomes of IVR in females remain uncertain.

Matrix metalloproteinases (MMPs) are zinc-dependent enzymes and the common feature is a zinc

**Table 1** Comparison of baseline characteristics between male and female

Age av.	HT	DM	HL	HDL av.	LDL av.	LDL/ HDL av.	HbA1c av.	FBS av.	CRP av.	TG av.	D-dimer av.	WBC av.	UA av.
Male	71.8 (59-89)	85.7% (24/28)	58.6% (17/29)	61.5% (16/26)	49.9 (38-57)	2.1 (1.0-5.1)	6.4 (5.5-9.0)	141.2 (82-269)	0.61 (0.06-3.33)	129.9 (63-286)	1.14 (0.36-3.99)	6.7 (3.8-9.7)	5.9 (2.4-8.2)
Female	72.1 (60-80)	81.8% (9/11)	88.9% (8/9)	55.5% (5/10)	48.5 (38-57)	2.0 (1.2-2.6)	6.8 (5.6-8.2)	145.1 (86-239)	0.39 (0.08-0.91)	120.7 (64-213)	0.67 (0.48-0.94)	7.6 (4.5-11.0)	4.9 (3.4-6.1)
P value	0.98	0.50	0.15	0.73	0.73	0.29	0.69	0.91	0.25	0.89	0.76	0.06	0.78

Age av.: Age average, HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, HDL: High Density Lipoprotein (mg/dl), LDL: Low Density Lipoprotein (mg/dl), HbA1c: Hemoglobin A1c (%), FBS: Fasting blood sugar (mg/dl), CRP: C-reactive protein (mg/dl), TG: Triglyceride (mg/dl), D-dimer: (μg/dl), WBC: White blood cell (×10<sup>9</sup>/L), UA: Uric Acid (mg/dl)

**Table 2** Comparison between cases with positive and negative DWI findings after CAS

Age av.	M:F	Pre-CAS		Post- CAS		BB T1 HIA	Symp- tomat- ic	HT	DM	HL	HDL av.	LDL av.	LDL/ HDL av.	HbA1c av.	FBS av.	CRP av.	TG av.	D-dimer av.	WBC av.	UA av.
		MMP-9 av.	MMP-9 av.	MMP-9 av.	MMP-9 av.															
DWI-positive 13 cases	71.5 (59-80)	6:7 (160-1540)	676.9 (-)	450.7 (-)	69.2% (9/13)	83.3% (10/12)	61.5% (8/13)	66.7% (6/9)	75.0% (9/12)	46.8 (31-74)	93.5 (56-134)	2.04 (1.2-3.4)	6.47 (5.2-8.2)	142.8 (86-213)	0.15 (0.07-0.32)	120.5 (64-159)	1.01 (0.36-2.04)	6.7 (5.4-9.6)	4.81 (2.4-6.2)	
DWI-negative 33 cases	72.3 (62-89)	28:5 (19-1040)	415.0 (-)	309.6 (-)	60.6% (20/33)	85.7% (24/28)	51.5% (17/33)	65.5% (19/29)	50.0% (12/24)	50.8 (26-64)	102.1 (51-208)	2.1 (1.0-5.1)	6.58 (5.1-9.0)	142.0 (82-269)	0.76 (0.06-3.33)	131.0 (57-286)	1.03 (0.22-3.99)	7.1 (4.5-11.0)	6.06 (3.4-8.3)	
P value	0.83	0.04	0.051	0.30	0.82	0.59	0.60	0.84	0.86	0.14	0.42	0.83	0.90	0.79	0.65	0.33	0.80	0.61	0.61	

av.: Average, M: Male, F: Female, CAS: Carotid Artery Stenting, MMP-9: Matrix metalloproteinase-9 (ng/ml), BB T1 HIA: Black-Blood T1 High Intensity Area, HT: Hypertension, DM: Diabetes Mellitus, HL: Hyperlipidemia, HDL: High Density Lipoprotein (mg/dl), LDL: Low Density Lipoprotein (mg/dl), HbA1c: Hemoglobin A1c (%), FBS: Fasting blood sugar (mg/dl), CRP: C-reactive protein (mg/dl), TG: Triglyceride (mg/dl), D-dimer: (μg/dl), WBC: White blood cell (×10<sup>9</sup>/L), UA: Uric Acid (mg/dl)

**Table 3** Comparisons of findings for male and female patients

	Symptomatic cases before CAS	pre-CAS MMP-9 av. (ng/ml)	DWI-positive after CAS	BB HIA (+) before CAS	BB HIA (+) in DWI-positive	DWI-positive in Symptomatic cases	DWI-positive & BB HIA in Symptomatic cases
Male	55.9% (19/34)	428.1	17.6% (6/34)	69.7% (23/33)	83.3% (5/6)	26.3% (5/19)	21.1% (4/19)
Female	50.0% (6/12)	661.7	58.3% (7/12)	50.0% (6/12)	66.7% (4/7)	50.0% (3/6)	33.3% (2/6)
P value	0.76	0.04	0.04	0.28	0.43	0.39	0.66

ion in the active centre. MMPs are known to be present in tissues, cells, blood and can digest extracellularly proteins, e.g. collagen, elastin, proteoglycan, fi-

bronectin. MMPs are biomarkers of coronary progressive arteriosclerosis<sup>4,5</sup>, because MMPs expressed in coronary plaques and increased in coronary unstable plaques<sup>6</sup>. MMPs are also related to Alzheimer disease, Parkinson disease and brain tumors<sup>28,30</sup>.

Among MMPs, gelatinase group (gelatinases) are Matrix metalloproteinase-2 (MMP-2) and Matrix metalloproteinase-9 (MMP-9). Gelatinase group (gelatinases) have the ability to active pro-inflammatory agents and to digest collagen type IV, tight junction proteins (TJPs). They facilitate to across the endothelium by leukocyte. Both the abilities of Gelatinase group (gelatinases) consequently lead to the spread of the inflammatory process<sup>19,20</sup>. This inflammatory process is associated with neuronal damage and apoptosis.

The difference with MMP-2 and MMP-9, MMP-9 has a heavier molecular weight than MMP-2 due to the carbohydrate residues attached to the enzyme during the post-translating processing. Besides the structural difference, in animal models of acute ischemic stroke, the serum activity of MMP-9 increased, however, the activity of MMP-2 does not change<sup>19</sup>. MMP-2 increases in later phase of cerebral infarction<sup>19</sup>. MMP-9 has potential to be related with carotid artery stenosis and prognostic factor of acute ischemic stroke<sup>7,20,23,26,27</sup>. Moreover, vulnerable plaques in patients for early CEA revealed a remarkable increase MMP-9 activation<sup>24</sup>. We speculate that MMP-9 may reflect not only arteriosclerosis but also fragility of carotid plaque. As mentioned above, we investigated serum MMP-9 for carotid artery stenosis in this study.

In this study, we used only distal balloon protection with Carotid Guardwire™ for the CAS procedure, because each protection method gives rise to a different rate of embolic complications<sup>23</sup>. Asymptomatic DWI-positive findings had about 21-54% after CAS<sup>2,3</sup>.

In our series, asymptomatic DWI-positive findings had 28.2% (13/46), acceptable and no cases had symptomatic DWI-positive findings.

MMP-9 for Pre-CAS and DWI-positive findings group tended to be high in comparison with Pre-CAS and DWI-negative findings group in this study. MMP-9 for Pre-CAS and DWI-positive findings in females was statistically higher than Pre-CAS and DWI-positive findings in males. However, MRI BB findings were not associated with DWI findings after CAS, although High

**Table 4** Comparisons of DWI findings and Pre-CAS MMP-9 between male and female patients

	Pre-CAS MMP-9 in females av. (ng/ml)	Pre-CAS MMP-9 in males av. (ng/ml)	P value
DWI-positive after CAS	812.9 (590-1340)	518.3 (160-1540)	0.045
DWI-negative after CAS	450.0 (250-1040)	408.8 (19-969)	0.76
P value	0.06	0.79	

Intensity Area (HIA) on BB MRI T1 weighed image is recognized as risk of ischemic stroke for CAS<sup>29</sup>. The reason may be that the ratio of BB MRI T1 HIA was high. 63% (29/46) of patients had HIA on BB MRI T1 in our study. This suggests that the risk difference of ischemic stroke for CAS exists in BB MRI T1 HIA group. MMP-9 may become one indicator of cerebral infarction after CAS in BB MRI T1 HIA group.

Females are fundamentally at lower risk of arteriosclerosis and stroke due to anti-arteriosclerotic effects of estrogen than males. Indeed, ischemic stroke is greater in males than females until 65 years, however, females have an equal number of strokes as males after the age of 65, relatively early. In females, coronary artery diseases are delayed by 10-15 years in comparison with males<sup>28</sup>. In this study, there was no gender difference in age. Therefore, we speculate that carotid arteriosclerotic change in females tend to worsen in a short period of time in comparison to males and may reflect high MMP-9.

Post-CAS MMP-9 was collected from an aspiration catheter just before deflation of the distal balloon after stenting to reflect the influence of CAS, nevertheless, Post-CAS MMP-9 and DWI-positive findings group had no tendency to be high compared with Post-CAS and DWI-negative findings group. MMPs, specifically MMP-9 levels following stroke are associated with disruption of the blood brain barrier (BBB) followed by ischemic edema and increased risk of hemorrhagic complications<sup>19,20,22</sup>. We presumed that Post-CAS MMP-9 did not increase due to no large cerebral infarction and hemorrhagic complications after CAS, although DWI-positive findings had 28.2%.

The limitations of this study include retrospective design and small number of patients.

We need more cases, particularly, female case and

prospective design to investigate this study.

Accumulating data suggest that increased MMP-9 is associated with cerebral infarction leads to neuronal damage, BBB disruption followed by cerebral edema and reperfusion injury.

Therefore, MMP-9 inhibitor has been noting as a therapeutic target in ischemic stroke for years. In future, MMP-9 inhibitor may contribute to prevent arteriosclerosis and ischemic stroke from worsening.

## Conclusion

Serum Pre-CAS MMP-9 levels in females have higher correlation with increased DWI-positive findings after CAS than in males. This result indicate that high serum MMP-9 may have a potential risk of ischemic stroke for CAS. CAS requires performing meticulous procedures, especially in females.

## Author contributions

All authors revised the manuscript, approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Conflicts of Interest

The authors declare that they have no conflict of interests.

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