Modic changes in the lumbar spine: exploring their association with abdominal aortic calcification as a potential indicator of systemic arherosclerosis

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Modic Changes in the Lumbar Spine: Exploring Their Association with Abdominal Aortic Calcification as a Potential Indicator of Systemic Atherosclerosis

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■ BACKGROUND: **This was a cross-sectional study on the correlation between abdominal aortic calcification (AAC) and Modic changes (MC). Little is known regarding the etiology of MC in the lumbar spine. Currently, insufficient vascularization of the endplate has been proposed to contribute to the appearance of MC. Our objective was to investigate whether AAC, a marker for a poor vascular status, is associated with MC in patients suffering from degenerative disc disease.**

■ METHODS: **Radiologic images of patients (n = 130) suffering from degenerative lumbar disc disease were reviewed. Type and severity of MC were assessed using magnetic resonance images, and severity of AAC was evaluated using computed tomography images or fluoroscopy. Both items were dichotomized into minimal and relevant grades. The correlation between them was studied using Spearman's correlation test, with age as a covariate.**

■ RESULTS: **Of the patients, 113 (87%) demonstrated MC (31% type I, 63% type II, and 6% type III) (55% relevant grade), and 68% had AAC (44% relevant grade). Spearman statistical analysis revealed that AAC was correlated with age ($P < 0.001$), whereas MC were not ($P = 0.142$). AAC severity was significantly correlated with MC, remaining so after age adjustment ($P < 0.05$). While MC type I lacked correlation with AAC, MC type II were significantly correlated with AAC (0.288, $P = 0.015$); however, this association lost significance after adjusting for age ($P = 0.057$).**

■ CONCLUSIONS: **AAC and MC (mainly MC type II) are associated, indicating that reduced blood supply or even a poor systemic vascularization status due to atherosclerotic disease may play a role in the formation of MC. Future studies focusing on the etiology of MC should pay more attention to patients' vascular status and determinants of abdominal aorta calcification.**

INTRODUCTION

Low back pain (LBP), with a lifetime prevalence of 60%–90%, is the leading cause of work-related disability and imposes a heavy socioeconomic burden.[1,2] LBP has many causes, yet one of the most prominent is degeneration of the intervertebral lumbar disc.[3] Even though the exact origin of disc degeneration remains to be elucidated, it is generally considered to be an age-related process.[4,5] Interestingly, recent evidence suggests that it is also related to insufficient blood supply to the lumbar spine,[6,7] as well as abnormal serum lipid status.[8,9] Together, this evidence raises the question whether a poor vascular status may contribute to disc degeneration (DD).

In agreement with this line of reasoning, abdominal aortic calcification (AAC), which is an important marker of subclinical atherosclerosis and a representative of the vascularization state in the whole body, was reported to appear simultaneously with DD on X-ray films or computed tomography (CT) examinations.[4,10,11] Moreover, it was reported that the severity of AAC was associated with the pre-DD or absence of DD.[4,12] In addition, AAC was also associated with other degeneration markers such as disc height loss[13] and lumbar osteophytes.[11] The nutrient supply of the

Key words
- Abdominal aorta calcification
- Low back pain
- Magnetic resonance imaging
- Modic changes

Abbreviations and Acronyms
AAC: Abdominal aortic calcification
CT: Computed tomography
DD: Disc degeneration
LBP: Low back pain
MC: Modic changes
MRI: Magnetic resonance imaging

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Citation: World Neurosurg. (2024) 184:e503-e510. https://doi.org/10.1016/j.wneu.2024.01.157

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

intervertebral disc, which is avascular, mainly comes from the diffusion of the endplate. Reduced blood supply to the endplate due to atherosclerosis eventually makes the intervertebral disc more susceptible to injury and degeneration,[14-17] and could thus induce DD.[18]

Furthermore, a more anatomy-based theory was proposed, grounded on the finding that atherosclerosis of the abdominal aorta mostly occurs around the bifurcation[12]—the area where the sacral arteries, which supply the lower lumbar segmental arteries, originate. It was hypothesized that arterial plaque formation in the abdominal aorta artery directly hinders the blood supply of the vertebral endplates.

As of today, it remains unknown how poor blood supply of the vertebral endplate can be recognized. Nonetheless, it is feasible that such endplate changes are visible on magnetic resonance imaging (MRI), for example, as Modic changes (MC), which are a representation of bone marrow and cartilage endplate signal changes.[19] Even though the etiology of MC is still poorly understood, some evidence suggests that the occurrence of MC is related to endplate tears,[20,21] microfractures caused by mechanical stress,[22,23] autoimmune reactions,[20] the presence of low virulence bacterial infection (*Propionibacterium acnes*),[24,25] and fat metabolism.[26,27] Moreover, clinical studies have shown that MC commonly occur at L4-L5 and L5-S1 levels,[28,29] which coincides with the blood supply position of the lumbar or sacral artery. Together, the evidence presented suggests that MC can be a marker for poor vascularization of the endplate.

Based on the above analysis, the hypothesis that MC are associated with AAC as a representative of an adverse (systemic state) vascularization is proposed. At present, no study has demonstrated the role of AAC in the occurrence and development of MC. The aim of this study is to evaluate the correlation between AAC and MC, in order to give insight in the pathogenesis of MC.

METHODS

Study Population

For an ongoing study in our center a cohort of patients that received instrumented surgery for degenerative lumbar disease between November 1, 2005, and November 1, 2013, was selected with consent of the medical ethics committee.[30] All these patients had an MRI (1.5 or 3.0 T) and CT/X-ray film of the lumbar spine available. Patients were excluded if they were younger than 18 years. The patients without a CT/X-ray film or MRI were also excluded from evaluation.

Radiologic Assessment of MC and AAC

The presence and type of MC were scored by 2 independent reviewers (W.L., C.V.L.) according to Modic et al.[31] The severity of MC was categorized according to the percentage of the area of abnormal signals in the entire vertebral body area in 4 grades (**Table 1**, **Figure 1**).[32] Abdominal aorta calcification was scored on CT, using the modified score of both Kiel et al.[33] and Turgut et al.,[34] or on X-ray images using the modified assessment approach of Jie et al.[35] The severity of AAC was evaluated and categorized into 4 grades (**Table 2**, **Figure 2**).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY). The associations between MC and AAC were evaluated using a Spearman correlation analysis. Outcome data were additionally corrected for age using partial correlation analysis with MC and AAC as variables.

RESULTS

Characteristics of the Study Population

A total of 130 patients were included (**Figure 3**). In this sample, 50% of the included patients was male and the mean age of patients was 59 ± 12 years. Dichotomization of patients by age was performed at the cutoff point of 60 years. The younger group (<60 years) and the older group (≥60 years) accounted for 48% and 52%, respectively (**Table 3**).

Prevalence of MC

A total of 113 (87%) patients demonstrated MC, of which the majority (63%) displayed Modic type II changes (**Table 3**). In one-third of the patients, the severity of MC was grade 1, and in almost half of the patients grade 2 MC were present; 18% demonstrated a grade 3. The severity of MC was also evaluated in a dichotomized manner: The combination of all patients with grade 0 and 1 was determined as "minimal" severity, which was present in 45% of patients. Thus, 55% of patients demonstrated "relevant" MC (grade 2 and 3).

Prevalence of AAC

AAC was evaluated on CT images in 102 patients, and on X-ray images in 28 patients. Eighty-eight (68%) of the 130 patients had AAC. Severity of calcification was scored as grade 1 in one-third, as grade 2 in almost half, and grade 3 in 22% of the patients (**Table 3**). Severity of AAC was also evaluated in a dichotomized manner: combining grade 2 and 3 was considered "relevant" AAC, which was present in 44%.

Correlation Between MC, AAC, and Age

Abdominal aorta calcification was correlated with age (0.544, $P < 0.001$), while MC were not (0.129, $P = 0.142$) (**Table 4**). Both the classification in 4 grades and the dichotomized data demonstrated a strong correlation between AAC and MC after adjusting for age ($P < 0.05$) (**Table 5**). When MC type I and MC type II were statistically analyzed separately, MC type I were not correlated with AAC (**Table 6**), while MC type II were significantly correlated with AAC (4 grades) before adjusting for age (0.288, $P = 0.015$). A

Table 1. The Modic Changes Grading Score

Grade	Modic Changes
0	No Modic signal changes
1	<25% of vertebral height
2	25%–50% of vertebral height
3	>50% of vertebral height

Severity: minimal = grade 0 + grade 1; relevant = grade 2 + grade 3.

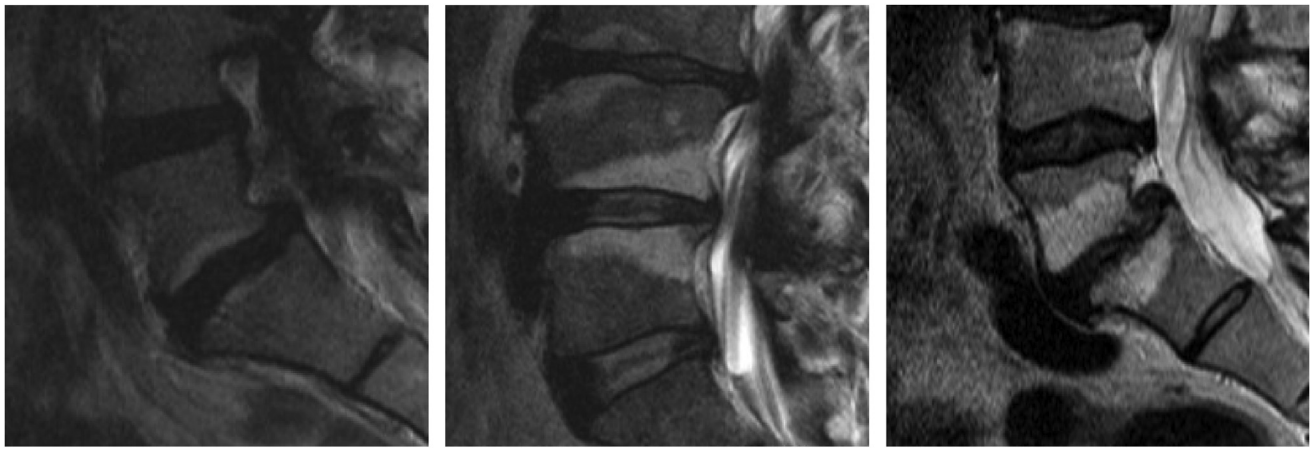

Figure 1. MC grade 1 (less than 25% of the vertebral body), grade 2 (between 25% and 50% of the vertebral body), and grade 3 (more than 50% of the vertebral body) on T2-weighted MRI.

similar trend was seen for MC type II after correcting for age, but significance was not reached ($P = 0.057$, Table 7).

DISCUSSION

The results of this study demonstrate a positive association between Modic changes and abdominal aorta calcification. In the literature, MC are described as a local phenomenon, focusing on edema, inflammation, and fatty bone marrow transformation near the endplate.[26,31] These pathologic features suggest that the affected vertebral unit is in a vulnerable state. The demonstrated association of AAC and MC indicates that a reduced blood supply likely plays a role in the abovementioned vulnerable state. Calcifications in the abdominal aorta (AAC), and possibly a reduced blood flow in the segmental lumbar arteries (supplying the L1-L4 vertebral bodies), or middle sacral arteries (supplying the L5 vertebral body) will reduce blood supply to the corresponding lumbar bone marrow and endplate.[7,36] Reduced blood supply to the endplate could subsequently lead to insufficient nutrient diffusion of intervertebral discs, thereby making them more vulnerable for damage.[37] Ultimately, the damage may induce the premature occurrence of lumbar intervertebral disc degeneration.[4,38] Under the mechanical shearing force, microfractures and even herniation of intervertebral disc tissue are more probable to occur, likely resulting in a local inflammatory response and bone marrow edema,[22,31,39] which is presented as MC type I on MRI. In a later stage, poor vascular status of the endplate is likely to lead to degenerative fatty and fibrotic changes which are seen in endplates as MC type II[26,40] (Figure 4).

Table 2. The AAC Grading Score

Grade	Radiologic Features of Abdominal Aorta
0	No calcific deposits in front of the vertebra (Figure 2A, 2B)
1	Small scattered calcific deposits filling <1/3 of the longitudinal wall of aorta (Figure 2C, 2D)
2	Moderate number of scattered calcific deposits filling ≥1/3, but <2/3 of the longitudinal wall of aorta (Figure 2E, 2F)
3	Massive nubby calcific deposits filling ≥2/3 of the longitudinal wall of the aorta calcified (Figure 2G, 2H)

Severity: minimal = grade 0 + grade 1; relevant = grade 2 + grade 3.

Literature yields evidence that MC are not only associated with a local reduced blood supply, but also with systemic factors that are associated with vascular insufficiency. Studies suggest that in addition to local arterial stenosis, atherosclerosis-related parameters such as body mass index,[41,42] serum lipid levels,[9,42-44] and apolipoprotein L1,[45,46] which represent systemic vascular status, are associated with DD, lumbar disc herniation, and LBP. Coincidently, many studies confirmed that MC are closely related to DD and LBP.[22,31,47-49] Hence, it is reasonable to speculate that the systemic vascular status plays a role in the etiology of the presence of MC (Figure 4).

It is well established that the condition of blood vessels such as the aorta is likely to deteriorate with age,[12,50,51] and the degenerative findings of the spine are also increasing with normal aging.[5,52-54] Age can be a potential confounding factor in assessing the association of AAC with DD.[54] This study demonstrated that age was associated with AAC but not with MC. Hence age was considered as a possible confounder and thus incorporated as a covariate in the analysis of our study. Nonetheless, the correlation calculated in this study between AAC and MC remained significant after correcting for age.

According to previous studies, MC type I are more likely to represent an acute state and often occur in young individuals.[26,55] While the incidence of MC type II has been shown to increase with age, especially in patients ≥50 years.[56,57] Therefore, a stronger

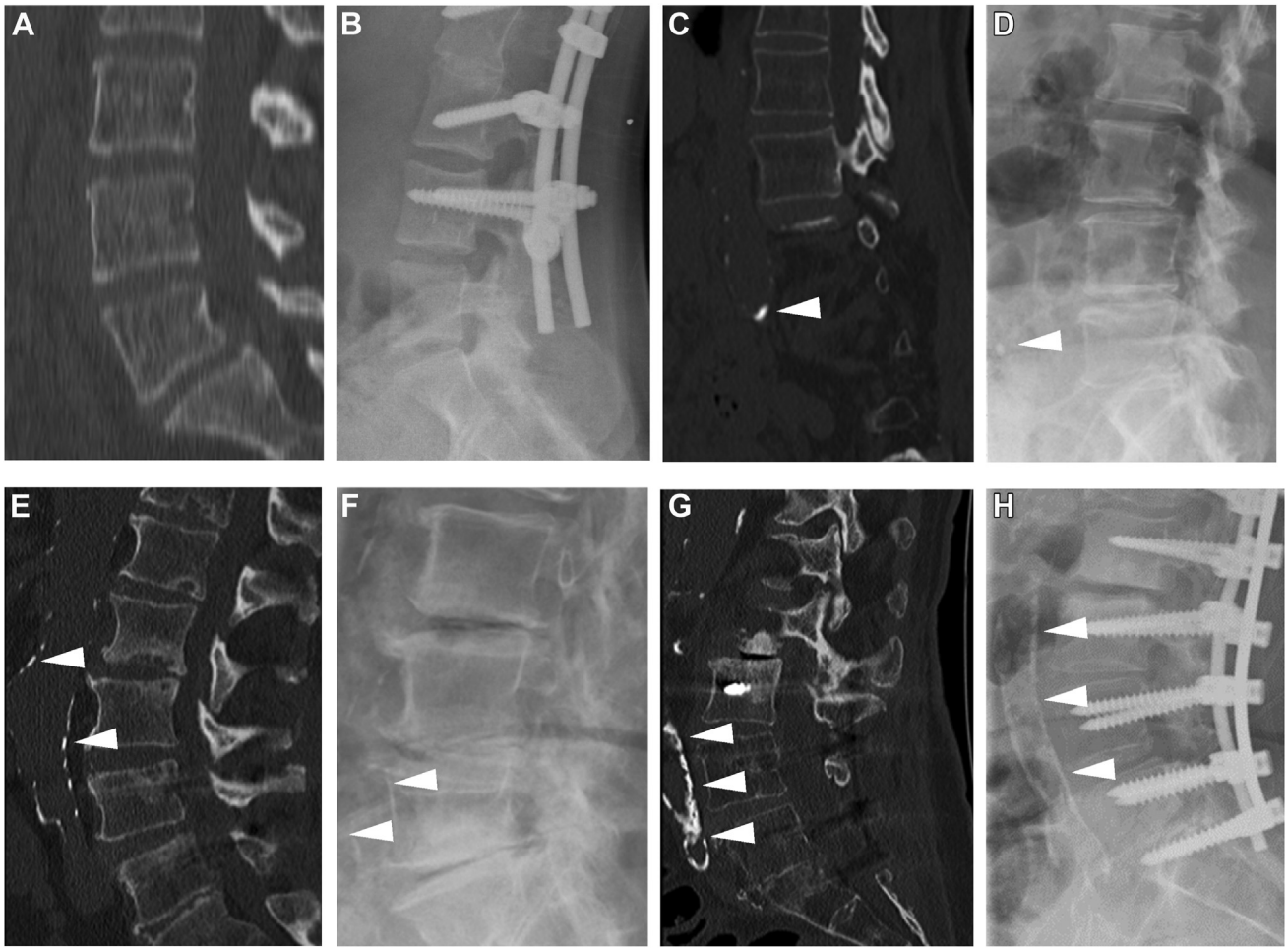

Figure 2. Sample images from a study population showing abdominal aortic calcification patterns (*arrows*) assessed for different severity grades. (**A, B**) No calcification in the abdominal aorta, grade 0. (**C, D**) Few scattered calcific deposits filling the aorta in front of the vertebra, grade 1. (**E, F**) Moderate number of scattered calcific deposits filling the aorta in front of the vertebra, grade 2. (**G, H**) Massive nubby calcific deposits filling the aorta in front of the vertebra (pipe shape), grade 3.

correlation between MC type 2 and AAC was expected compared to type 1. However, MC1 could occur as a consequence of AAC since a chronically degenerated endplate is likely more vulnerable to a low-grade infection or reactive inflammation, which will result in MC type 1. Nevertheless, this will probably co-occur with AAC less often than the degenerative changes associated with MC type 2. An animal study has shown that high levels of serum cholesterol, which can cause atherosclerosis, lead to accumulation of fat in the vertebral bone marrow and endplate. This accumulation will further lead to macrophage infiltration, inflammatory reaction, and vascular disturbances, manifested as MC, and accelerate vertebral unit ischemia and degeneration.[58] When stratifying the analysis based on the type of MC in this study, the correlation only remained, in line with the abovementioned reasoning, positive for MC type II and even near significant after adjusting for age. A plausible reason for the weak correlation in these subgroups is the limited sample size of this study. In addition, previous studies have confirmed that MC commonly first occur as MC type I.

Taken together, this study specifically raises the possibility that reduced blood supply, in addition to physical compression an inflammation, can make the endplate more susceptible to injury and degeneration, and thereby likely plays a role in the pathophysiology of MC. Nevertheless, the associations demonstrated in this study between AAC and MC are not of causal nature. Therefore the suggested pathophysiology should not be interpreted as strong proof that atherosclerosis causes MC, but instead as a logical theory based on the associations found in this study and other literature.

A possible limitation of this study is that the available radiologic material only allowed us to focus on AAC displayed on the CT/X-ray films. More precise imaging techniques should be sought to show the blockage of the branch arteries by the AAC and the blood flow velocity of the lumbar supplying arteries. Moreover, it would

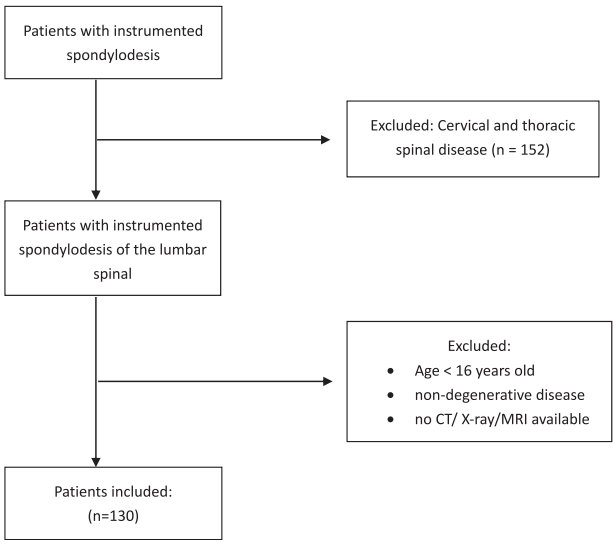

Figure 3. Flowchart illustrating patient selection for inclusion in the study.

have been very interesting to also consider parameters representing systemic vascular and lipid status. Furthermore, the number of patients that were studied was limited, and no definite judgment can be made on differences for MC type I and II. Therefore, future studies with large samples and multi-factor analysis are needed.

CONCLUSIONS

This study showed that AAC was associated with the presence and severity of MC. This sheds a new light on the etiology of MC and its implications for spine degeneration. Future studies should further specify the direction of this relationship in a longitudinal observational study and are warranted to evaluate determinants of insufficient vascularization in relation to degeneration of the spine.

KEY POINTS

- The severity of Modic changes on MR images, abdominal aortic calcification on CT or x-ray images and their associations were studied in a cohort of patients suffering degenerative disc disease.
- The majority of MC was type II. 55% of patients was assessed as 'relevant' severity of MC and 'minimal' severity was assessed as accounting for a larger proportion of AAC. Abdominal aorta calcification was correlated with age, while MC were not.
- The severity of AAC was significantly correlated with MC, and the correlation remained after adjusting for age.

Table 3. Descriptive Characteristics of the Study Population (N = 130)

Characteristics	N (%) or Mean (SD)
Age, years	59 ± 12
<60	63 (48%)
≥60	67 (52%)
Sex	
Male	65 (50%)
Female	65 (50%)
MC	
All types	113 (87%)
No MC	17 (13%)
Type I	35 (31%)
Type II	71 (63%)
Type III	7 (6%)
Severity of MC	
Grade 0	17 (13%)
Grade 1	41 (36%)
Grade 2	52 (46%)
Grade 3	20 (18%)
Minimal	58 (45%)
Relevant	72 (55%)
AAC	
All grades	88 (68%)
No AAC	42 (32%)
Severity of AAC	
Grade 0	42 (32%)
Grade 1	31 (35%)
Grade 2	38 (43%)
Grade 3	19 (22%)
Minimal	73 (56%)
Relevant	57 (44%)

SD, standard deviation; MC, Modic changes; AAC, abdominal aorta calcification. Minimal = grade 0 + 1; relevant = grade 2 + 3.

- When stratifying the data for type of MC, only MC type II was significantly correlated to AAC.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Wensen Li: Writing — original draft. **Niek Djuric:** Writing — review & editing. **Christa Cobbaert:** Writing — review & editing. **Carmen L.A. Vleggeert-Lankamp:** Methodology, Project administration, Supervision, Writing — review & editing.

Table 4. Severity and Correlation of MC and AAC in Age Groups

	Age, years		Total		
	<60	≥60	n (%)	Correlation	*P* Value
MC					
Minimal	30	28	58 (45)	0.129	0.142
Relevant	33	39	72 (55)		
AAC					
Minimal	49	24	73 (56)	0.544	<0.001
Relevant	14	43	57 (44)		

Table 5. Correlation Between MC and AAC

		Spearman Correlation		Partial Correlation Adjusting for Age	
MC	AAC	Coefficient	*P* Value	Coefficient	*P* Value
Minimal/relevant	Minimal/relevant	0.214	0.015	0.181	0.040
Grade 0, 1, 2, 3	Minimal/relevant	0.221	0.012	0.175	0.048
Minimal/relevant	Grade 0, 1, 2, 3	0.273	0.002	0.246	0.005
Grade 0,1,2,3	Grade 0, 1, 2, 3	0.282	0.001	0.239	0.006

Table 6. Correlation Between MC Type I and AAC

		Spearman Correlation		Partial Correlation Adjusting for Age	
MC type I	AAC	Coefficient	*P* Value	Coefficient	*P* Value
Minimal/relevant	Minimal/relevant	0.164	0.346	0.141	0.428
Grade 0, 1, 2, 3	Minimal/relevant	0.114	0.515	0.034	0.847
Minimal/relevant	Grade 0, 1, 2, 3	0.179	0.304	0.157	0.376
Grade 0, 1, 2, 3	Grade 0, 1, 2, 3	0.170	0.328	0.095	0.592

Table 7. Correlation Between MC Type II and AAC

		Spearman Correlation		Partial Correlation Adjusting for Age	
MC Type II	AAC	Coefficient	*P* Value	Coefficient	*P* Value
Minimal/relevant	Minimal/relevant	0.192	0.108	0.120	0.321
Grade 0, 1, 2, 3	Minimal/relevant	0.228	0.056	0.163	0.178
Minimal/relevant	Grade 0, 1, 2, 3	0.265	0.025	0.213	0.077
Grade 0, 1, 2, 3	Grade 0, 1, 2, 3	0.288	0.015	0.229	0.057

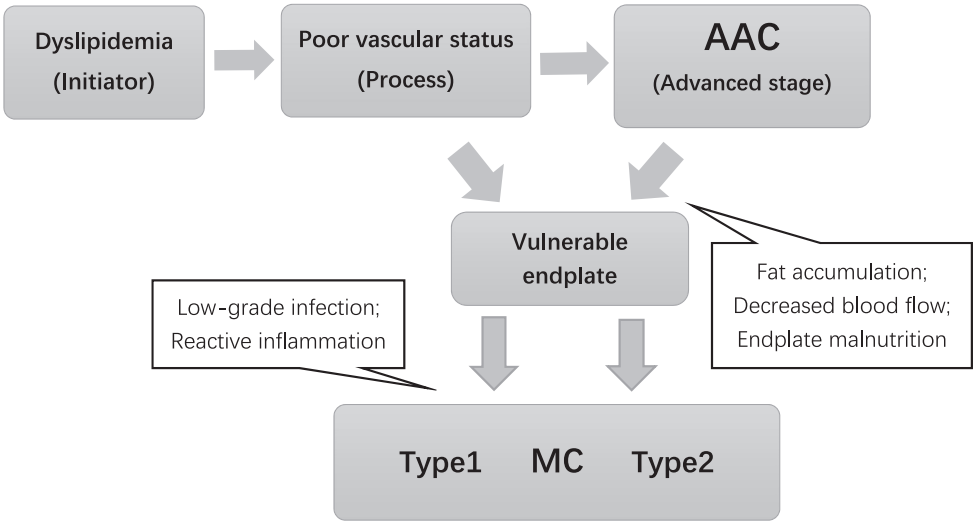

Figure 4. Flowchart illustrating the hypothesis interaction mechanism between dyslipidemia, poor vascular status, AAC, and MC.

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Conflict of interest statement: This work was supported by China Scholarship Council (CSC) and the Department of Neurosurgery, Leiden University Medical Center (LUMC), The Netherlands. Wensen Li received support from both funding agencies. The CSC and LUMC did not play a role in the design of the study, data collection or analysis of the data. For the remaining authors none were declared.

Received 7 September 2023; accepted 26 January 2024

Citation: World Neurosurg. (2024) 184:e503-e510. https://doi.org/10.1016/j.wneu.2024.01.157

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