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Review

Dual effect of Vascular Calcification in Abdominal Aortic Aneurysm Progression: A Narrative Review from Multi-Scales

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ABSTRACT: Abdominal aortic aneurysm (AAA) is a degenerative vascular disease with a high mortality rate of rupture, yet effective pharmacological interventions to delay its progression or prevent rupture remain unavailable. Vascular calcification (VC), a prominent pathological feature of AAA, exhibits a paradoxical role. Clinical and biomechanical studies confirm that VC exerts a dual effect: it accelerates AAA progression by inducing local stress concentration, while simultaneously providing mechanical stability through global load-sharing effect. This functional paradox may stem from a dynamic imbalance between anabolic and catabolic processes at the cellular and molecular levels. Specifically, microcalcification is mediated by the osteogenic transition of vascular smooth muscle cells (VSMCs), whereas the osteoclastic transformation of macrophages contributes to the ultimate matrix degradation. Furthermore, the impacts of vascular aging, sex differences, and metabolic dysregulation between VC and AAA are briefly summarized. This review systematically synthesizes multi-scale evidence to elucidate the dual role of VC in AAA progression, proposing a non-linear dynamic trajectory linking microcalcification initiation to macrocalcification maturation during aneurysm progression. Finally, it also emphasizes that future research should shift from assessing static calcification burden toward dynamically monitoring the metabolic activity of microcalcification, as well as discussing emerging therapeutic targets. This perspective offers new insights for early risk stratification and precise intervention in AAA.

Keywords: vascular calcification, aneurysm, minerals, metabolism, calcinosis

1. Introduction

Abdominal aortic aneurysm (AAA) is a life-threatening vascular condition, associated with high risk of abrupt rupture, characterized by localized dilation of the infrarenal aorta consistently exceeding 1.5–fold increase from normal size or above 3 cm [1]. With a prevalence up to 8% in men over 65 years of age, AAA rupture carries a catastrophic mortality rate exceeding 80%, making it a leading cause of death in the elderly population [2, 3]. Although advances in open and endovascular surgical techniques have improved the management of large aneurysms, no effective pharmacological therapies currently exist to halt the progression of small AAAs [4]. This gap highlights a critical unmet clinical need and underscores the importance of elucidating the underlying

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pathological mechanisms behind the progression of AAA [5].

AAA predominately affects the elderly population and is closely associated with aortic senescence. Pathological hallmarks of AAA include degradation of the extracellular matrix (ECM), loss of vascular smooth muscle cell (VSMC) contractile function, and inflammatory infiltration [5, 6]. Vascular calcification (VC), a hallmark of vascular aging [7], is increasingly recognized as a cellular-regulated and active pathological feature that contributes to AAA progression across multiple scales [8–12], rather than just a degenerative deposition. VC represents an active form of vascular remodeling driven by the synergistic action of VSMCs and macrophages. It is characterized by the deposition of hydroxyapatite crystals (HA) within the vessel wall. Based on its anatomical location, VC is classified into intimal, medial, and valvular calcification [13]. Intimal calcification is characterized by lipid plaque buildup and inflammation, which is often confined to the lumen or the endothelial layer, contributing to occlusive arterial disease. Medial calcification, also known as arteriosclerosis, involves the calcification of the elastic fibers and VSMCs within the tunica media [13]. This form of calcification is often observed in conditions such as chronic kidney disease (CKD), diabetes mellitus (DM), and aging. Medial calcification has a predilection for arteries less prone to atherosclerosis; it is rarely seen in the coronary arteries but does affect the abdominal aorta [14, 15]. While intimal calcification is associated with plaque instability and advanced atherosclerosis, medial calcification, which directly impacts the elasticity and aortic wall biomechanics, is hypothesized to play a more direct role in promoting aneurysm formation and expansion [12, 16].

Clinical significance of VC in the AAA context presents a paradox: while higher calcification burden often correlates with increased risks of aneurysm growth, rupture, and cardiovascular mortality [17–20], extensive calcification has paradoxically been linked to stability or report no significant correlation [21, 22], suggesting a dual role of calcification in AAA that is not yet fully understood. This complex and contradictory role of calcification in AAA pathogenesis is evident across multiple scales. Advances in imaging technology and the integration of machine learning algorithms now allow for precise quantification and early detection of calcification, providing new insights into the mechanisms of mineralization in AAA formation [23–25].

Biomechanically, calcific deposits exert a dual effect in AAA sac stabilization: they concentrate local stresses and induce strain heterogeneity [8, 26], thereby increasing the risk of wall failure, while in some cases reducing global wall stress through load-sharing mechanisms [27]. At the molecular and cellular level, phenotypic switching of VSMCs plays a crucial role in calcification formation in AAA, especially the osteogenic phenotype, which is capable of promoting mineralization similar to osteoblast cells. Simultaneously, the formation of osteoclast-like cells (OLCs) is another key process involved in VC, responsible for mineral resorption and vascular remodeling [28]. The OLCs are predominantly derived from the monocyte-macrophage lineage [9, 10, 12, 28, 29]. However, the ultimate outcome of VC is significantly influenced by the net balance between anabolic (osteoblast-like VSMCs) and catabolic (osteoclast-like macrophages) activity, and these processes are regulated by key transcription factors and signaling pathways, and are further influenced by factors including vascular aging, sex differences, and metabolic disorders such as CKD and diabetes [30, 31], which complicate the role of calcification among different backgrounds.

Therefore, this review systematically integrates these multidimensional aspects—ranging from detection and clinical significance to biomechanical impacts and molecular mechanisms—to clarify the clinical and translational relevance of calcification in AAA progression and to outline future research directions.

2. Radiological Detection and Quantification of Vascular Calcification

Conventional radiologic modalities such as X-ray plain film and ultrasonography, while accessible for initial screening of calcification, are limited by their low sensitivity and a susceptibility to misdiagnosis [32, 33]. Similarly, reliable visualization of VC is constrained by the inherent technical limitations of magnetic resonance imaging (MRI) [34–36]. In contrast, computed tomography (CT) is considered the gold standard for detecting calcification due to its high-resolution capability for visualizing tissue mineralization, which enables precise characterization of its location, morphology, and distribution [36, 37].

Calcification detectable by non-contrast CT typically represents established macrocalcification, defined as calcium deposits with a diameter exceeding 500 μm. Conventional metrics like Agatston score heavily rely on macrocalcifications on CT [38]. Precise characterization of calcification morphology and spatial distribution, particularly within the aneurysm neck or access vessels, is crucial for preoperative planning of endovascular aneurysm repair (EVAR) [15, 18, 39]. Microcalcification (diameter <50 μm) signals early-stage active mineralization and remains challenging to visualize using routine clinical CT [40, 41]. Emerging artificial intelligence (AI) algorithms, such as 3D nnU-Net or an integrated AI pipeline are revolutionizing the

quantification of calcification, enabling automated segmentation and super-resolution imaging that surpasses clinical CT limitations [24, 42]. AI-enhanced image post-processing optimizes workflow efficiency by reducing scan times, lowering radiation doses while maintaining higher resolution [24, 42, 43]. In addition, advancements in imaging technology have introduced techniques such as spectral CT, three-dimensional CT reconstruction, and virtual non-contrast (VNC) imaging, all of which substantially enhance the accuracy and specificity of VC detection [38, 44, 45].

Accumulating evidence has increasingly linked VC to both AAA progression and EVAR prognosis [18, 46]. Consequently, the clinical paradigm for VC assessment is shifting from simple detection to nuanced risk stratification and informing therapeutic decision-making. Crucially, calcium deposition during AAA progression is a non-linear dynamic process. Early-stage active microcalcification is closely linked to elastin integrity, yet it may progressively evolve into dynamically stable or inert macrocalcific deposits during aneurysm dilation [47, 48]. While CT enables clinicians to intuitively visualize and qualitatively assess established macrocalcification, positron emission tomography/computed tomography (PET/CT), utilizing specific radiotracers, allows for the quantification of inflammatory and metabolic activity *in vivo* [49]. This approach has significantly advanced the understanding of the pathological status and metabolic landscape underlying AAA.

Moving beyond static morphological assessment of established macrocalcification provided by CT, ^{18}F-sodium fluoride (^{18}F-NaF) PET/CT offers new insights to visualize and quantify the metabolic activity and spatial distribution of microcalcification [49]. These molecular alterations, manifesting as increased radiotracer uptake, often precede the macroscopic structural changes detectable by CT monitoring. Consequently, ^{18}F-NaF imaging holds promise for early identification of high-risk regions of aortic wall vulnerability, as well as for serving as a sensitive surrogate endpoint to assess early therapeutic efficacy of anti-calcific interventions [23, 25]. However, clinical implementation of ^{18}F-NaF PET/CT remains constrained by its high cost and radiation burden [38, 50], which requires further validation and technological advancement for future clinical routine application. Importantly, limited by its spatial resolution and the potential for false positives in inflammatory background without mineralization, the results of ^{18}F-NaF PET/CT necessitate cautious interpretation and validation through multi-scale methods.

Recently, preclinical research has turned to advanced imaging modalities, including micro-CT, near-infrared fluorescence (NIRF), and light-sheet fluorescence microscopy (LSFM), to facilitate high resolution of microcalcific identification and the exploration of underlying mechanisms. Micro-CT exhibits exceptional sensitivity and specificity of VC in animal models, capable of resolving early-stage microcalcifications (1–10 μm) both *in vivo* and *ex vivo*. The additional application of respiratory gating technology may facilitate longitudinal VC monitoring *in vivo* by minimizing motion artifacts [38, 51], with ^{18}F-NaF micro-PET/CT systems providing simultaneous support for qualitative and quantitative molecular imaging of active calcification.

Complementing the structural imaging, the NIRF technique, utilizing bisphosphonate-based probes (e.g., OsteoSense) targeting HA, can detect active focal micro-mineralization with nanomolar sensitivity [50]. Although its spatial resolution is inferior to micro-CT, its superior molecular sensitivity allows for the precise quantification of osteogenic activity during the pre-calcific stage [50]. Moreover, LSFM offers a unique advantage in resolving the spatial interplay between surrounding inflammatory cells and the calcified region by employing specific immunofluorescence labeling [51]. LSFM achieves high-resolution 3D construction of calcific microenvironment; however, its application is limited to *ex vivo* analysis due to limited tissue penetration depth and the requirement of invasive tissue processing like tissue optical clearing [51]. In summary, these diverse imaging modalities delineate distinct spatiotemporal features of VC. Summary of different methods and detailed information are presented in Figure 1 and Table 1 respectively. In preclinical models, respiratory-gated micro-CT facilitates longitudinal monitoring of VC progression, whereas NIRF and LSFM are instrumental in characterizing the early metabolic activity and microenvironmental landscape at the nascent stage. While non-contrast CT remains the gold standard for serial detection of VC clinically, integration of AI algorithms and spectral imaging techniques holds significant promise for future precise, early identification of VC *in vivo*.

3. Clinical Association and Biomechanical Interpretation of Calcification in AAA

The clinical association between VC and AAA presents a significant paradox: while some evidence indicates calcification is a risk factor for progression and rupture, other studies suggest it may have a stabilizing role. This seemingly contradictory role can be rationally explained by the dual biomechanical effects that calcification exerts on the aortic wall.

3.1 Evidence and Mechanisms of Calcification as a Risk Factor

Table 1. Comparison of key imaging modalities for VC: From Clinical to Preclinical scale.

Imaging Techniques	Target& Spatial Resolution	Key Strength/Implication	Limitations
CT **Dual Energy/ Spectral CT [38]**	Target: Macrocalcification Resolution: >500μm	1) Gold standard for detecting established calcification clinically, with specific anatomical structure, non-invasive, and accessibility 2) Quantification metrics: standardized quantification via the Agatston Score, LACS, and ACI *etc.* [66, 155, 156]. 3) Advanced spectral capabilities: SPCCT: facilitates material decomposition, clear differentiation of iodine, gadolinium, and calcification in a single scan [44]. DECT: generates VNC images, eliminating the need for separate non-contrast scan and reducing radiation exposure by approximately 23% [45].	1) Blooming artifacts: high-density calcification appears larger than reality, potentially obscuring the lumen 2) Unable to identify early-stage microcalcification 3) Radiation exposure
^{18}F-NaF PET [40]	Target: Active microcalcification Resolution: low (~4-5 mm), but enhanced by CT fusion	1) Unique ability to identify active microcalcification before structural change in clinical modalities 2) Functional localization: when fused with CT, it precisely localizes molecular calcification activity to specific anatomical regions 3) Prognostic value: high uptake correlates with disease progression and clinical events.	1) Poor intrinsic spatial resolution 2) Accessibility & Cost: expensive and longer scan times limit routine use 3) Cumulative radiation exposure for PET/CT 4) Lack of universally established quantitative thresholds for clinical risk stratification.
Micro-CT [38, 51]	Target: Macro- and micro-calcification Resolution: high, < 10-50 μm *in vivo*; ~1 μm *ex vivo*	1) High resolution mapping: enables non-destructive, 3D structural analysis of intact vessel segments 2) Longitudinal monitoring: respiratory gating techniques allow for *in vivo* tracking of microcalcification in animal models 3) Combining with specific molecular probe offers microstructural and metabolic insight	1) Motion artifacts *in vivo*, and poor contrast of soft tissue 2) Long scan times, high radiation exposure and requirement for deep anesthesia 3) Unable to visualize crystalline lattice of micro-calcification
LSFM [51]	Target: Cellular level Resolution: high, sub-micron	1) 3D Imaging without physical sectioning: Provides rapid, high-resolution 3D reconstruction of *ex vivo* tissue or organ with minimal photodamage 2) Spatial cellular specificity: visualizes specific cell types (e.g., macrophages, VSMCs) associated with calcification via specific fluorescent labeling	1) *Ex vivo* only: typically requires tissue clearing, complex sample preparation 2) Depth penetration: limited by light scattering Only preclinical use
NIRF [50]	Target: Molecular activity of micro- and macro calcification (e.g.,MMPs, Hydroxyapatite) Spatial Resolution: Moderate to low (mm level, depth-dependent) Molecular Resolution: nmol level	1) Molecular specificity and sensitivity: utilizes targeted probes (e.g., bisphosphonates like OsteoSense) to visualize active mineral deposition or enzymatic activity (MMPs) with high specificity 2) High signal-to-noise ratio: minimized background autofluorescence in the NIR window	1) Limitation of depth penetration, only *ex vivo* and *in vitro* research 2) Lack of anatomical information, provides functional signal only 3) Difficult to quantify calcification burden

Abbreviations: CT, computed tomography; LACS, length-adjusted calcification score; ACI, aortic calcification index; SPCCT, spectral photon-counting CT; DECT, dual-energy CT; VNC, virtual non-contrast; ^{18}F-NaF PET, ^{18}F-sodium fluoride positron emission tomography; LSFM, light-sheet fluorescence microscopy; VSMCs, vascular smooth muscle cells; NIRF, near-infrared fluorescence; MMPs, matrix metalloproteinases.

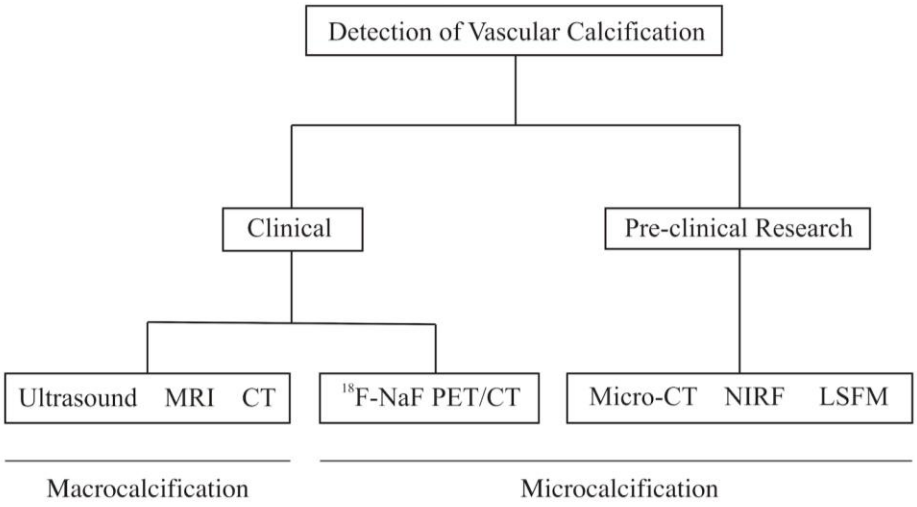

Figure 1. Summary of methods in detection of AAA calcification. Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; ^{18}F-NaF PET, ^{18}F-sodium fluoride positron emission tomography; LSFM, light-sheet fluorescence microscopy; NIRF, near-infrared fluorescence.

Multiple clinical studies support a positive correlation between higher calcification burden and the presence, progression, and risk of AAA rupture. For instance, each unit increase in the calcium score of the abdominal aorta and iliac arteries is positively correlated with an increase in aortic size [52], and Joshi et al. found that Agatston score is significantly higher in the aneurysmal segment than the non-aneurysmal regions in the same AAA patients and control populations [53]. A higher coronary artery calcium score (CACS) is also independently associated with a higher prevalence of AAA in high-risk populations [54]. Regarding rupture prediction, a higher Abdominal Aortic Calcification-8 (AAC-8) score is a significant multivariate predictor of symptomatic or ruptured AAA, with each point increase conferring an odds ratio of 1.34 for rupture risk [17]. More specifically, focal discontinuity of mural calcification demonstrated a high specificity for predicting rupture, particularly when combined with other signs like a hyper-attenuation crescent in aneurysms larger than 5 cm [55].

Mechanistically, calcific deposits compromise wall integrity by creating concentrations of local stress. The elastic modulus of calcific plaques is much higher than that of the surrounding aortic wall tissue; this material property mismatch creates significant stress gradients at the calcium–matrix interface [56, 57]. A study found that stiffening of aortic sac wall is positively correlated with elastin degradation and mineralization, ultimately reducing AAA wall strength [58]. Finite element analyses (FEA) have proposed that the presence of calcification leads to a mean 174% increase in localized peak strain, an 18.2% rise in peri-calcific tissue stress [8], and elevated peak wall stress (PWS) [59–61] within the aneurysm sac. Notably, these FEA results are computational predictions based on specific parameters, rather than *in vivo* measurements, underscoring the necessity of mechanical testing for validation. Nevertheless, hemodynamic disturbance, such as fluctuation of high blood pressure, is likely to amplify local stresses, accelerating aortic wall dilation and ultimately predisposing the aneurysm to rupture.

3.2 Evidence and Mechanisms of Calcification as a Stabilizing Factor

Contrary to the above findings, a considerable body of evidence paradoxically links a higher calcification burden to delayed AAA expansion and reduced intervention risk, suggesting a biomechanically stabilizing role. A study reported that patients with small AAAs and over 50% circumferential wall calcification exhibited a significantly lower mean annual growth rate and a reduced multi-adjusted risk ratio for surgery compared to those with less calcification [19]. Klopf et al. further found that higher infrarenal aortic calcification volumes and Agatston scores were correlated with slower-progressing AAA [22]. A recent secondary linear analysis of the Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^{3}CT) supports this finding [62]. This inverse correlation was also confirmed by Nakayama that a calcification index ≥ 2.74% was negatively associated with expansion rates, independent of AAA diameter [63]. A case report even described a Behçet's syndrome patient with a large AAA managed solely with immuno-suppression, in whom the aortic size reduced alongside

the development of circumferential wall calcification over a 20-year follow-up [64].

The biomechanical explanation for this protective association is the global load-sharing capacity of calcification. Although calcification increases stress locally, under certain circumstances—particularly when deposits are located in concavely shaped wall regions and form a continuous, uninterrupted rim—they can share part of the tension load borne by the vessel wall. Patient-specific computational models have shown that this mechanism can reduce the average wall stress by 9.7–59.2% [27].

Therefore, the biomechanical impact of calcification on AAA stability is double-edged: it can compromise wall integrity by inducing strain heterogeneity and predisposing the calcium-fibrous matrix interface to failure under tension [57, 65]; meanwhile, it may also confer partial stability by reducing overall sac stress [27].

3.3 Deciphering the Paradox: The Influence of Spatial Distribution and Dynamic Activity

Lindholt et al. demonstrated that a continuous calcification ring (>50% circumference) [19], or a calcification index ≥2.74% proposed by Nakayama exerts a protective effect by restricting aneurysm expansion [63]. However, standardizing these thresholds is complicated by the variability and reproducibility in different CT imaging protocols. While the Agatston score is the gold standard for coronary calcium [66], its application in routine non-gated abdominal CT is limited by motion artifacts, partial volume effects, and variations in slice thickness and tube voltage (kVp), compromising the consistency of quantification [67]. Therefore, quantitative metrics derived solely from total calcium burden on different CT, may lack the requisite precision to serve as a universal biological threshold. To address this, future research should adopt standardized CT scanning protocols, including uniform slice thickness, tube voltage, and reconstruction algorithms, combined with AI-assisted segmentation to minimize measurement heterogeneity. Furthermore, a comprehensive evaluation system integrating 'calcification morphology–metabolic activity–biomechanical properties' should be established, rather than depending on a single threshold.

Beyond the heterogeneity in objective measurements, Maier et al. attributed aneurysm deformation to the reduced distensibility of calcified tissue, which forces the aneurysm to expand anisotropically [27]. This may ultimately be associated with the asymmetric growth pattern and divergent rupture risks observed between saccular and fusiform aneurysms. Furthermore, substantial continuous calcification may absorb global aneurysmal stress as a load-bearing structure [27, 68], counterbalancing the wall fragility induced by focal microcalcifications [57]. Yet, establishing a precise tipping point, where global load-bearing effects override local stress concentrations, remains unexplored in current biomechanical simulations.

Divergent modeling predictions stem primarily from variable material parameterization and spatial location of calcific deposits across different computational fluid dynamics (CFD) studies [27, 60]. Explicit or implicit simulation of calcification differentially impacts the compatibility and interactive forces between itself and the aneurysm wall [27]. Therefore, establishing clinical calcification thresholds requires integrating patient-specific contexts rather than relying solely on mechanical parameters. Vascular aging is associated with diffuse matrix stiffening; therefore, we speculate that the focal stiffness mismatch is likely less pronounced in the rigid aortas of elderly patients compared to the compliant aortas of younger individuals. Moreover, according to Laplace's law, spotty calcification may present focal stress concentration within a relatively low global tension in early stage, small aneurysm. Extensive macrocalcification may act like a rigid shell, constraining late-stage, significant aneurysm expansion; nevertheless, it may also compromise structural integrity by reducing the wall failure property of calcification-tissue interface decoupling, rendering AAA more at risk of rupture [57].

Beyond the aggregate calcium load and measurement variability, the clinical and biomechanical impact of calcification is critically influenced by its spatial distribution and dynamic activity. Research indicates that well-distributed calcification clusters across the aneurysmal wall, as opposed to a smaller number of aggregates, are associated with a lower rupture risk [26]. Intact AAAs are more likely to exhibit a continuous, uninterrupted rim of circumferential calcification compared to ruptured ones [69]. This suggests that the spatial distribution pattern of calcification is significantly associated with whether it ultimately manifests as "disruptive" or "stabilizing." Studies have shown that aortic wall thickness and intraluminal thrombus (ILT) also link with spatial distribution of calcification. Spatial wall thicknesses of expanded AAA are heterogeneous; regions of calcific deposition typically exhibit wall thickening, while sites prone to rupture demonstrate significant local thinning, reaching as low as 0.23 mm [70]. Clearly, when rigid calcific deposits juxtapose with the thinned wall regions, they exhibit a precarious structure within the aneurysm sac. FEA with variable wall thickness remodeling has shown that the inclusion of calcification significantly alters the global stress distribution, with stress concentrations increased at the calcification periphery and within thinned wall regions [61, 71].

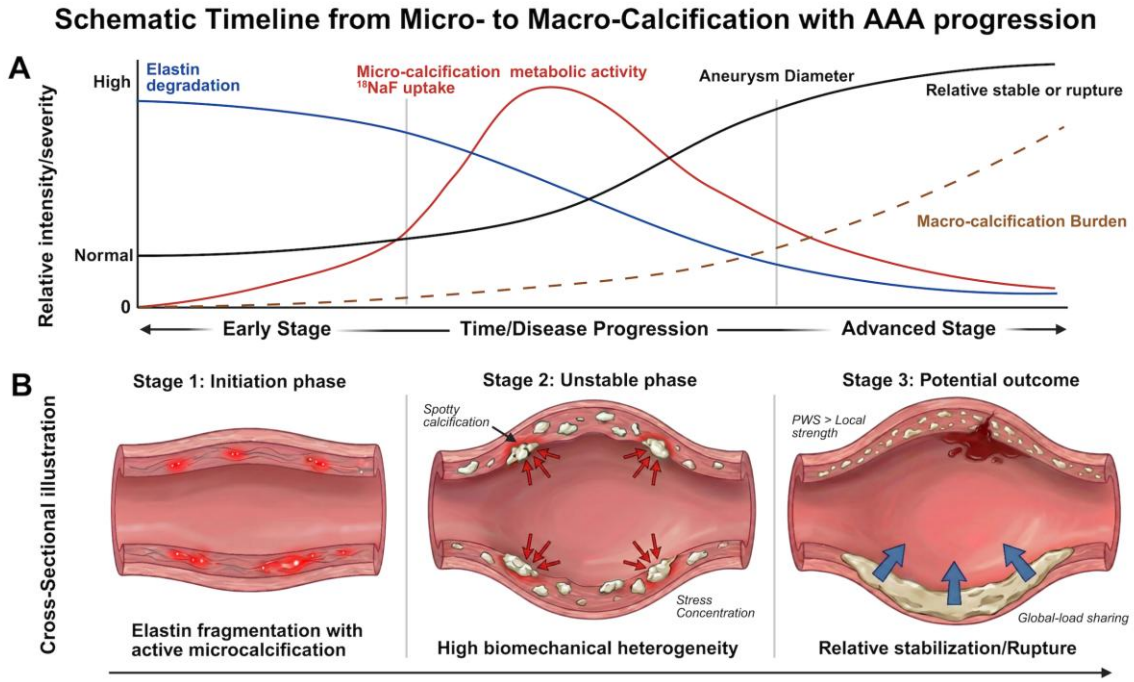

Figure 2. Schematic timeline illustrating the temporal evolution from microcalcification to macrocalcification during AAA progression. (A) Dynamic interplay between pathological features and disease severity over time. The graph illustrates that metabolic microcalcification activity (red line), indicated by ^{18}F-NaF uptake, peaks during the intermediate, unstable phase of aneurysm expansion. This activity precedes the accumulation of extensive macrocalcification burden (brown dashed line) and clinically apparent aneurysm dilation (black line). Notably, the initiation of microcalcification deposition coincides with the early phase of elastin degradation (blue line); as the disease advances, the extent of microcalcification progressively decreases in parallel with the loss and degradation of elastic fiber integrity [47]. **(B)** Cross-sectional representations of the aortic wall corresponding to three distinct evolutionary stages. **Stage 1 (Initiation Phase):** This phase is characterized by elastin fragmentation and the onset of active microcalcification within the vessel wall, representing a pre structural metabolic stage. It highlights that metabolic changes and early ECM remodeling precede morphological dilation. These metabolic alterations can be validated *via in vivo* molecular imaging, such as ^{18}F-NaF or ^{18}F-FDG PET/CT [25, 49], or *ex vivo* NIRF bisphosphonate probes [48, 50]. **Stage 2 (Unstable Phase):** This stage represents a window of structural heterogeneity. The formation of spotty calcifications, combined with ongoing elastin degradation, creates a highly heterogeneous structure [149]. This stiffness mismatch may generate focal stress concentrations (red arrows), contributing to biomechanical instability and rapid expansion, as predicted by CFD simulations based on aortic imaging [27, 57]. This stage can be serially assessed by non-contrast CT clinically or micro-CT in murine models, with active microcalcification detectable by ^{18}F-NaF PET/CT. **Stage 3 (Potential Outcome):** The progression from an unstable phase to a potential outcome is influenced by the net balance between anabolic and catabolic processes. This equilibrium is modulated by upstream regulators and modifiable risk factors, such as vascular aging, local oxidative stress, smoking, and other metabolic disorders (e.g., CKD or diabetes)—ultimately contributing to differences in wall stress and strength [12, 47, 48]. This stage is typically monitored by sequential clinical CT or longitudinal micro-CT in animal models. The transition to extensive macrocalcification may contribute to global load sharing (blue arrows) and relative wall stabilization; however, rupture remains a risk if PWS exceeds local wall strength. Abbreviations: AAA, abdominal aortic aneurysm; CFD, computational fluid dynamics; ^{18}F-NaF, ^{18}F-sodium fluoride; PET/CT, positron emission tomography/computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; NIRF, near-infrared fluorescence; ECM, extracellular matrix; CKD, chronic kidney disease; PWS, peak wall stress; CT, computed tomography; micro-CT, micro-computed tomography.

Beyond the static burden and spatial distribution of established macrocalcification, the metabolic activity of early-stage microcalcification offers deeper insights into the pathogenesis of AAA. As outlined in section 2, this shift in focus provides new perspectives for early interventional strategy. AAA with enhanced PET/CT metabolic signal uptake presents a noticeable change in biomechanical property [72]. Aortic segments underlying the ILT often have heightened ECM metabolism, which may subsequently predispose to wall weakness and microcalcification deposits [8, 60]. Such a microenvironment of local hypoxia and high mechanical stress may induce proactive VSMCs apoptosis and their osteogenic transdifferentiation [7], promoting AAA progression. While it may turn out that the impact of transition from micro- to macrocalcification on aneurysm growth is non-linear, conventional CT imaging only provides a static assessment of macrocalcification burden,

whereas molecular imaging with ^{18}F-NaF PET/CT can dynamically capture active mineralization [49, 73].

This active process may offer superior predictive value for AAA progression and rupture risk [40, 74]. Animal models have confirmed that increased ^{18}F-NaF uptake precedes substantial aortic expansion and strongly correlates with the final aortic size and aneurysm formation [25, 75]. The pivotal prospective Sodium Fluoride Imaging of Abdominal Aortic Aneurysms (SoFIA^3) study also found that AAA patients in the highest tertile of ^{18}F-NaF uptake experienced a 2.5–fold faster annual expansion rate and were nearly 3 times more likely to require repair or suffer rupture, compared to those in the lowest tertile [23]. All the above evidence shows that early microcalcification activity positively correlates with AAA presentation and may predispose to different AAA-related outcomes. These findings indicate that active, ongoing calcification processes—rather than just static calcified deposits—are a powerful indicator of AAA progression. Furthermore, a study has identified that while microcalcification is recognized as an early pathological hallmark of aneurysmal dilation, advanced progression was found to be associated with concomitant loss of both microcalcification and elastin [47]. This observation may reveal the non-linear dynamics between calcification and aneurysm progression: the early phase of aneurysm is characterized by active microcalcification, while as aneurysm advances with ECM-destructive remodeling, the microcalcific deposits may paradoxically diminish or consolidate into inert macrocalcification. To resolve the temporal sequence, we propose a 'three-stage hypothesis' delineating the non-linear dynamics of calcification throughout AAA progression (Fig. 2). Specifically, early-phase microcalcification precedes extensive aortic dilation and serves as a marker of underlying pathology, accompanied by inflammation and active metabolism. When microcalcification reaches its peak level during the advancing phase of AAA, as indicated by ^{18}F-NaF PET/CT, we hypothesize that upstream regulators and modifiable risk factors—such as vascular aging, local oxidative stress, smoking, and metabolic disorders (e.g., CKD or diabetes)—may further influence its transition to inert, biologically diffuse macrocalcification, or contribute to its gradual disappearance alongside increased aortic wall fragility. Biomechanically, this process can be quantified through CFD simulations, specifically by assessing PWS and global wall strength derived from aortic imaging or validated via *ex vivo* detection in animal models.

Table 2. Multi-dimensional Assessment of VC in AAA: From Static Burden to Dynamic Activity.

Assessment Dimension	Metrics/Methods	Key Clinical Findings	Biomechanical/Pathophysiological interpretation
1.Static Burden	Agatston score* AAC-8* calcification volume %calcification index* Visual assessment	**Risk Factor:** higher calcification burden is a risk factor for AAA prevalence, progression, and rupture [17, 52, 53, 55] **Stabilizing Factor:** rim calcification volume > 50% and higher calcification burden protect against AAA expansion and intervention risk [19, 22, 63]	**Increased local stress concentration:** Compliance mismatch between calcific deposits and surrounding wall tissue [8, 56, 57, 59–61] **Global load-sharing capability:** especially consider it an uninterrupted rim [27]
2.Spatial Distribution/ Morphology	Focal discontinuity *vs*. Continuous circumferential pattern	Focal discontinuity of calcific deposits combined with hyperattenuation crescent shows high specificity for predicting rupture [55] Continuous circumferential patterns are associated with stable, intact AAAs and low rupture risk [26, 69]	**The spatial pattern of calcification, beyond mere burden**, critically influences global wall stress distribution, with continuous dispersion being more protective [26, 27]
3.Dynamic Activity	^{18}F-NaF uptake: SUV*max TBR*max SUVmean	Preclinical studies：High uptake significantly precedes aortic expansion and AAA formation [25, 75] The pivotal SoFIA^{3}clinical trial：high ^{18}F-NaF uptake predicts advanced AAA expansion and adverse events [23]	Molecular imaging of microcalcification reveals ongoing disease activity and early pathophysiology, whereas CT scans represent "static scars"

Note. *Quantitative Agatston calcium scores were determined according to the method described by Agatston et al [66], as each calcification area ≥1 mm^2 with a density of ≥130 Hounsfield units (HU) could be calculated by summing all the scores from all slices.
*AAC-8 calcium score was a modified calculation of AAC-24, manually detected on a sagittal perspective corresponding to the areas in front of the lumbar vertebrae L1-L4, details are described by Schousboe et al [157].
*%calcification index was calculated as area of calcification defined as ≥ 130 HU in non-contrast CT, divided by ROI area of transverse slice, total calculated by averaged %calcification index of all slices in AAA sac [63].
*SUVs represent the standardized uptake values of tissue radiotracer, quantifying from regions of interest.
*TBRs are calculated as the tissue-to-background ratios, after correction for blood pool activity using the averaged mean SUVs.

In summary, we suggest that the dual role of calcification does not represent a genuine biological paradox, but rather reflects variations across different disease stages (early active microcalcification versus late stable macrocalcification) and distinct spatial patterns (focal versus continuous circumferential). Future risk assessment should integrate both metabolic activity and morphological features, rather than relying exclusively on static calcification burden. All clinical and biomechanical relevance are summarized in Table 2.

4. Molecular and Cellular Mechanisms Linking Calcification and AAA Pathology

4.1. Brief overview of VSMCs' plasticity and calcification in AAA

AAA is fundamentally characterized by the destruction of tunica media and extensive ECM remodeling. Recently, vascular calcification has been increasingly recognized as an active pathological feature of aneurysm formation and progression, rather than a passive degenerative process [4, 48]. Intimal calcification is typically initiated by inflammatory macrophages within lipid-rich plaques. In contrast, AAA-associated calcification occurs against a background of vascular aging and medial degeneration, intrinsically linking to VSMCs calcification and apoptosis [13, 16, 76]. Intact elastin functions as a natural inhibitor of mineralization; its degradation is often thought to facilitate calcium deposition [77], as Wanga et al. observed that microcalcification strongly correlates with severe elastin fragmentation in Marfan syndrome [48]. However, research found that in the mild-to-moderate stages of aneurysmal disease, microcalcification deposition occurs along intact elastin rather than elastin microfragments [47], whereas its content significantly diminishes in severe lesions. The above evidence suggests that microcalcification deposition may be non-linearly correlated with aneurysm progression.

While elastin and collagen degradation represent the final steps to weaken aneurysm wall, upstream alterations in the vascular microenvironment—such as metabolic imbalance, mechanical stress, oxidative stress, inflammation, and immune activation—determine the fate of VSMCs dedifferentiation. For example, as macrophage-like transition is prone to develop in lipid-rich and highly inflammatory niches, $LGALS3^{+}$ $CD68^{+}$ macrophage-like VSMCs actively secrete pro-inflammatory cytokines and matrix metalloproteinases (MMPs) to exacerbate chronic inflammation and ECM degradation within aneurysmal wall [78, 79]. While in response to mechanical stretch and transcription factor 21(TCF21) signaling, VSMCs may adopt a myofibroblast-like phenotype. These cells synthesize collagen and fibronectin in a compensatory attempt to repair the weakening aortic wall, contributing to adventitial fibrosis and potentially stabilizing the aneurysm [78, 79]. Moreover, the osteogenic transition of VSMCs under conditions of calcium-phosphate imbalance, oxidative stress or BMP signaling contributes to the final HA deposition [12, 16]. Importantly, KLF4, as the marker of VSMCs dedifferentiation, has been extensively involved in the above phenotypic transition.
In the context of VC, this review focuses on the osteogenic-like phenotypic transition of VSMCs and the osteoclast-like differentiation of macrophages, which could coactivate calcification in AAA progression. This phenotypic switching is further exacerbated by the dysregulation of intracellular mechanisms, including epigenetic modifications and calcium signaling imbalance. Ultimately, by activating of cell–ECM interactions, these processes may collectively increase vascular "brittleness," characterized by a loss of resilience and diminished mechanical strength, thereby contributing to AAA progression and rupture. Details of mechanisms are summarized in Figure 3.

4.2. Role of Osteogenic VSMCs Transition in AAA

While preservation of the contractile VSMCs phenotype inhibits aneurysm progression [78], recent studies highlight that the synthetic VSMCs phenotype, particularly the osteogenic VSMCs, significantly contributes to both AAA progression and VC [12, 75, 80]. This phenotypic shift is characterized by decreased expression of contractile proteins such as smooth muscle protein 22 α (SM22α) and α-smooth muscle actin (α-SMA), alongside upregulation of osteoblast markers, including bone morphogenetic protein 2 (BMP-2), which initiates upstream osteogenic signaling; alkaline phosphatase (ALP), an enzyme that facilitates mineralization by hydrolyzing pyrophosphate; and matrix proteins like osteocalcin (OCN) and osteopontin (OPN) that regulate HA deposition [78, 79]. Crucially, this transition is driven by key osteogenic transcription factors, such as runt-related transcription factor 2 (RUNX2), as the early master regulator initiating osteogenic lineage; Krüppel-like factor 4 (KLF4), as the marker reflecting the phenotypic plasticity level; and SRY-BOX transcription factor 9 (SOX9), which supports chondrogenic differentiation [78, 79]. Collectively, these changes promote abnormal vascular remodeling and HA deposition during vascular wall calcification.

RUNX2, a key transcription factor in bone metabolism, has been shown to play a critical role in AAA. VSMCs-specific deletion of RUNX2 markedly represses AngII-induced AAA formation and reduces associated microcalcification in mice [75]. Concurrently,

time-serial ^{18}F-NaF PET imaging demonstrated the predictive power of early microcalcification and subsequent AAA development, as the AngII-induced mice that were positive for ^{18}F-NaF uptake on day 7 subsequently developed dramatic aortic dilation, whereas the saline group and the uptake–negative group did not [75]. Moreover, the Smad2/3–RUNX2–miR-424/322 signaling axis has been reported to promote ECM degradation, microcalcification, and vascular wall remodeling in murine AAA models [81]. *In vitro* experiments confirm that Smad2/3–RUNX2 signaling regulates osteogenic transition in human VSMCs, contributing to upregulation of MMP-2/9 and vascular endothelial growth factor (VEGF), while siRNA-mediated RUNX2 knockdown alleviates micro-calcification in mice [81]. Interestingly, RUNX2 activation also induces its inhibitory regulator, miR-424, which in turn provides negative feedback on RUNX2 by targeting Smad3, and exogenous miR-322 mimics further alleviate AAA formation in mice [81]. This phenomenon implies that the physiological equilibrium between pro-calcific drivers (e.g., RUNX2) and endogenous inhibitors (e.g., miR-424) regulated by feedback mechanisms may influence macroscopic calcifying changes. After the change of pro-calcifying upstream, studies have also observed that HA deposits, as the end-product of VC, form proximal to sites of elastin fragmentation, with additional HA application exacerbating AngII-induced AAA formation *in vivo* [75]. While other runt-related transcription factors such as RUNX3 are upregulated in human AAA specimens and have been shown to promote VSMCs dedifferentiation and MMPs secretion via suppression of TGF-β1 *in vitro* [82], the correlation between RUNX3 and AAA formation requires further validation *in vivo*. SOX9, a key transcription factor in chondrogenesis, has been found to directly bind the runt domain of RUNX2, thereby inhibiting RUNX2 function and modulating osteogenic differentiation [83]. While this suggests a calcification-inhibiting effect, few studies have focused on the role of SOX9 in osteogenic differentiation in AAA.

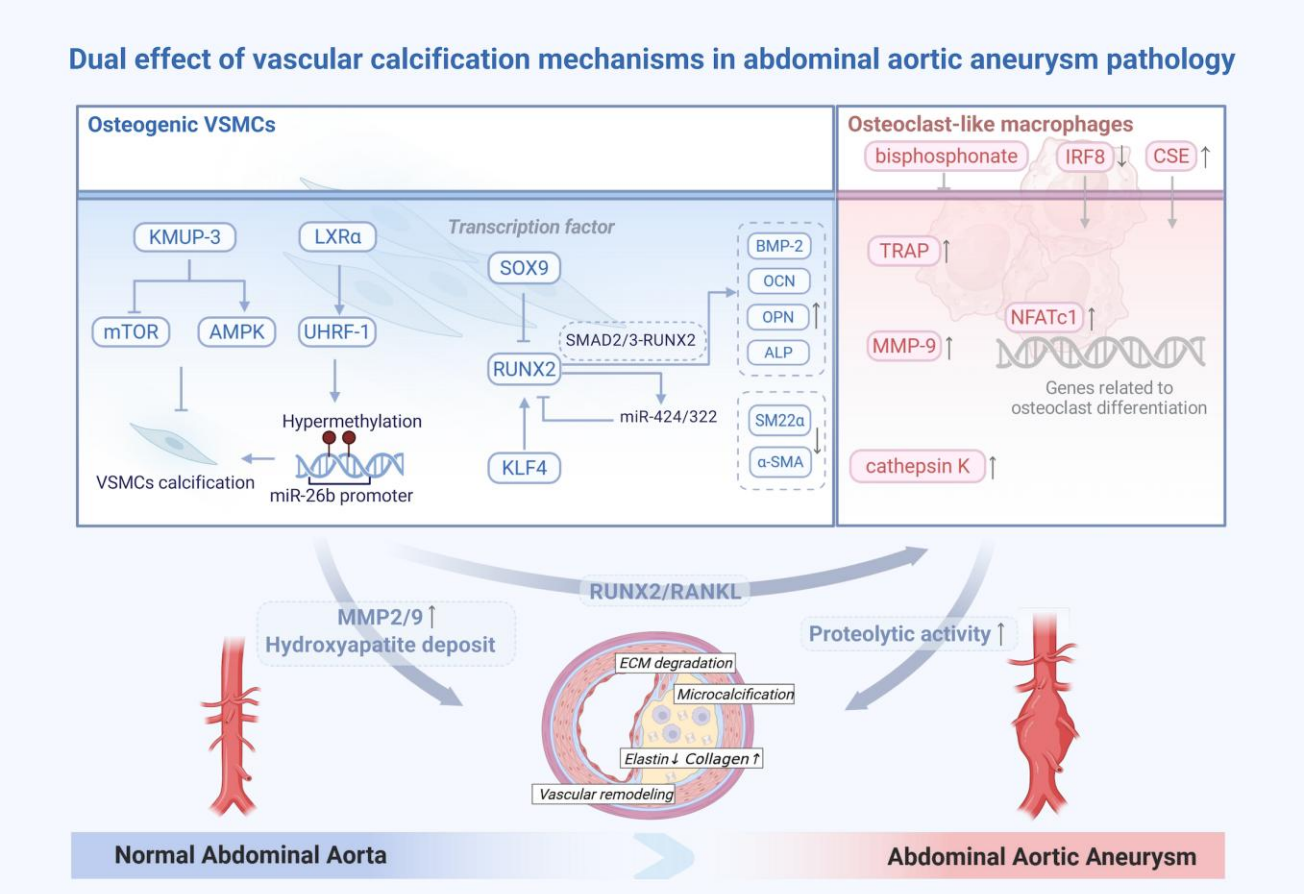

Figure 3. Schematic diagram illustrating the dual-effect mechanisms of VC in AAA pathology. This figure delineates two core cellular pathways underlying the dual effect of VC in AAA pathology: the osteogenic transition of VSMCs (left, anabolic) and the osteoclast-like differentiation of macrophages (right, catabolic). **Left:** The osteogenic transition of VSMCs integrates multiple signaling inputs. Upstream regulators such as LXRα promote this process through UHRF-1-mediated methylation of the miR-26b promoter, whereas the xanthine derivative KMUP-3 suppresses it by activating AMPK and inhibiting mTOR signaling. Such transition involves

the upregulation of key transcription factors, including RUNX2, KLF4, and SOX9, alongside the downregulation of contractile markers such as SM22α and α-SMA. Activation of the SMAD2/3-RUNX2 pathway subsequently induces the expression of osteogenic markers like BMP-2, OCN, OPN, and ALP. This phenotypic shift ultimately contributes to anabolism, leading to hydroxyapatite deposition within the vascular wall matrix. **Right:** Simultaneously, recruited macrophages differentiate into osteoclast-like cells. This differentiation is regulated by CSE and IRF8. It involves the upregulation of the key nuclear transcription factor NFATc1, and culminates in the expression of catabolic markers, including TRAP, MMP-9, and cathepsin K, which enhance proteolytic activity. **Pathway Crosstalk and Pathological Outcome:** A central feature of this mechanism is the crosstalk between the two pathways: osteogenic VSMCs promote macrophage osteoclast-like differentiation via the RUNX2-RANKL signaling axis. The dynamic imbalance and synergistic interaction between anabolism and catabolism collectively drive ECM degradation and remodeling, microcalcification formation, and ultimately contribute to AAA progression. **Abbreviations:** LXRα, Liver X Receptor α; UHRF-1, ubiquitin-like containing PHD and RING finger domains 1; KMUP-3, 7-[2-[4-(4-nitrobenzene)piperazinyl]ethyl]-1,3-dimethylxanthine; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; RUNX2, runt-related transcription factor 2;KLF4, Krüppel-like factor 4;SOX9, SRY-BOX transcription factor 9; SM22α, smooth muscle protein 22 α; α-SMA, α-smooth muscle actin; BMP-2, bone morphogenetic protein 2; OCN, osteocalcin; OPN, osteopontin; ALP, alkaline phosphatase; CSE, cigarette smoke extract; IRF8, interferon regulatory factor 8; NFATc1, nuclear factor of activated T cells cytoplasmic 1; TRAP, tartrate-resistant acid phosphatase; MMP-9, matrix metalloproteinase-9; RANKL, 'receptor activator of nuclear factor kappa-B ligand; ECM, extracellular matrix.

KLF4 has emerged as an indicator of VSMCs dedifferentiation level, with its elevated expression signifying a shift towards a synthetic phenotype [78, 79]. BMP2-regulated osteogenic differentiation is suggested to depend on intracellular cooperative binding of RUNX2 and KLF4 [84]; however, the precise upstream–downstream interactions within VSMCs' osteogenic transition remain unclear. Salmon et al. discovered that both KLF4 heterozygous whole-body knockout and VSMCs–specific KLF4 knockout mice exhibit significantly delayed formation of elastase- and AngII-induced AAA [85]. Furthermore, KLF4 deficiency was shown to alleviate elastin degradation and macrophage infiltration within aneurysm sac microenvironment, suppress inflammatory responses, and maintain the contractile phenotype of VSMCs [85]. Chromatin immunoprecipitation assays confirmed that KLF4 binds to the promoter regions of VSMCs contractile genes, directly regulating their expression [85]. These findings establish a foundation for further investigation into the role of KLF4 in regulating VSMCs' phenotypic transition. Recent studies have identified FAM3A, a cytokine-like protein with metabolic regulatory functions, as exerting a protective effect against AAA despite its widespread tissue expression [86–88]. FAM3A activates the TGF-β/Smad3 signaling pathway, promoting ubiquitination of KLF4 protein while suppressing its phosphorylation and nuclear translocation [88]. This negative regulation of KLF4 helps maintain the contractile phenotype of VSMCs and delays AAA formation. Similarly, Hu et al. identified PP2Acα, a key catalytic subunit of serine/threonine phosphatases in eukaryotes, as an upstream regulator of KLF4 protein ubiquitination [89]. Phenotypic rescue experiments confirmed that loss of PP2Acα leads to intracellular accumulation of KLF4, inducing synthetic phenotype transition in VSMCs and ultimately promoting the formation of BAPN-induced aortic dissection and PPE-induced AAA in mice [89]. However, it should be noted that PP2Acα is not an initial disease trigger, and its role in disease progression depends on induction by external risk factors.

In addition to these master transcription factors involved in osteogenic VSMCs phenotypic transition, there are complex intracellular signaling networks governing the change. For instance, loss of liver X receptor α (LXRα) function alleviates osteogenic VSMCs phenotypic switching during AAA development by downregulating ubiquitin-like containing PHD and RING finger domains 1 (UHRF-1)-mediated hypermethylation of the miR-26b promoter [90]. Lai et al. found that activation of mammalian target of rapamycin (mTOR) and β-catenin is linked to VSMCs phenotypic transition and calcification, while AMP-activated protein kinase (AMPK) activation exerts protective effects [91]. The xanthine derivative KMUP-3 was shown to inhibit VSMCs calcification by suppressing mTOR while enhancing AMPK signaling [91]. The neuron-derived orphan receptor-1 (NOR-1) has emerged as a potential driver of aneurysmal remodeling. Research found that NOR-1 exacerbates susceptibility to AngII-induced AAA by upregulating MMPs activity and ROS levels, thereby promoting elastin degradation [92]. However, NOR-1 overexpression in atherosclerosis mice has been shown to suppress vascular ectopic calcification [93]. This may suggest that NOR-1 serves as an upstream molecular switch driving VSMCs toward different phenotypes, future studies need to clarify whether it promotes a pro-inflammatory or macrophage-like phenotype while simultaneously repressing the osteogenic lineage.

In addition to intracellular signaling, extracellular cues within the pathological microenvironment also contribute to osteogenic differentiation. Elastic fiber fragmentation is a hallmark feature of AAA formation, and the deposition of calcium phosphate minerals onto elastic lamellae constitutes a key pathological event. The degradation of elastin by MMPs releases elastin-derived peptides (EDPs) or matrikines, which have been shown to actively promote the osteogenic differentiation of local

cells, thereby driving the calcification cycle. For example, elastase-derived elastin fragments (elastokines) induce osteogenic responses in VSMCs via binding to the S-Gal receptor, facilitating arterial calcification [94]. In addition, aberrant vascular stiffness induced by changes in ECM composition may drive the osteogenic transition in VSMCs via mechanotransduction pathways. As Ballester-Servera et al. observed a significant upregulation of lysyl oxidase (LOX) in calcified atherosclerotic plaques and aortic valves [95], they proposed that ECM characterized by aberrant collagen deposition could induce osteogenic differentiation in both VSMCs and valvular interstitial cells (VICs) by *in vitro* decellularized matrix exchange assays [95]. They further elucidated that overexpression of LOX could contribute to this phenotypic switching through ROS/H_2O_2-mediated oxidative stress, which can be significantly inhibited by mitochondrial-targeted antioxidants, such as mito-TEMPO [96]. LOX has canonically been regarded as a protective enzyme in AAA, essential for preserving structural integrity via ECM cross-linking [97, 98]. However, emerging insights have found its non-canonical biological properties, ranging from oxidative stress induction to transcriptional regulation, suggesting a more intricate and potentially paradoxical role of LOX in orchestrating aneurysmal formation and calcification [99–101]. Erythrocyte membrane fragments from intraplaque hemorrhage may further induce osteoblast-like differentiation in human VSMCs through nitric oxide-mediated pathways [102]. These membrane components colocalize with calcified regions and osteoblast-like cells in human atherosclerotic lesions, aortic valves, and AAA [102, 103]. Hyperphosphatemia represents another key pathological factor; under hyperphosphatemic conditions, miR-34a upregulation induces both VSMCs senescence and osteogenic differentiation [104].

4.3. Role of Osteoclastic Macrophage Differentiation in AAA

Alongside the osteoblast-like transition of VSMCs, a critical immune response involving the differentiation of macrophages into OLCs is implicated in AAA progression [6, 29]. Under pathological conditions, OLCs express tartrate-resistant acid phosphatase (TRAP), MMP-9, and cathepsin K—proteins that are absent in healthy aortic tissue but abundant in both human and experimental AAA tissues [10, 29]. Functionally, these OLCs exhibit heightened protease activity, contributing to ECM degradation and mediating the mineral resorption, thereby collectively compromising aortic wall integrity [10, 11]. Several pathological stimuli trigger this osteoclastic differentiation. Cigarette smoke extract (CSE) contributes to macrophage differentiation towards the osteoclast lineage, upregulating nuclear factor of activated T cells cytoplasmic 1 (NFATc1), TRAP, cathepsin K, and MMP-9, thereby enhancing proteolytic activity and accelerating aneurysm expansion *in vivo* [105]. This differentiation process is further exacerbated by metabolic stress, as a maternal high-fat diet epigenetically reprograms offspring macrophages toward an osteoclast-like phenotype by suppressing interferon regulatory factor 8 (IRF8) expression but enhancing NFATc1 signaling [106]. Furthermore, bisphosphonate treatment inhibits AAA formation in mice by suppressing osteoclastogenic differentiation, highlighting OLCs as a potential target for AAA pharmacotherapy [29].

Mechanistically, OLCs' differentiation is critically regulated by the receptor activator of nuclear factor-kappa B (RANK)/receptor activator of nuclear factor kappa-B ligand (RANKL) signaling pathway, which is central to bone metabolism and heavily implicated in AAA pathogenesis [11]. In AngII-induced AAA models, OLCs with increased RANKL expression have been observed, and RANKL neutralization suppresses AAA development [107]. Crucially, a direct crosstalk mechanism linking these two cell types has been identified: oxidative stress-induced osteogenic VSMCs promote the migration and differentiation of bone marrow-derived macrophages into OLCs via upregulation of RUNX2-RANKL expression. Conversely, RUNX2-knockout VSMCs show decreased RANKL expression, reduced OLCs numbers, and less calcification [108, 109].

4.4. Discussion of Mechanistic Crosstalk and Future Directions

In summary, the mechanisms linking calcification to AAA pathology are multifaceted, reflecting a dynamic imbalance between anabolic and catabolic processes. On the one hand, the osteogenic phenotypic transition of VSMCs, driven by key transcription factors such as RUNX2 and KLF4, promotes an anabolic state that facilitates the deposition of metabolically active microcalcifications. On the other hand, macrophages undergo catabolic differentiation into OLCs via the RANKL/RANK signaling pathway, enhancing proteolytic activity that promotes wall remodeling and mineral resorption. Although calcification has traditionally been associated with stenotic diseases, such as atherosclerosis, emerging evidence indicates that aneurysmal dilation is also accompanied by dynamic calcium deposition [23, 25]. Preclinical studies corroborate this, demonstrating that the metabolic activity of early microcalcification, in particular, positively correlates with subsequent AAA development [25, 75]. VSMCs transdifferentiation contributes to diverse cellular landscape of AAA, osteogenic VSMCs-mediated

activation of bone marrow-derived macrophages (BMDMs) through the possible RUNX2-RANKL axis constitutes a distinct, synergistic pathway that may influence anabolic-catabolic imbalance. It is critical to distinguish whether the OLCs involved in this crosstalk are recruited BMDMs or the dedifferentiated VSMCs that have acquired a macrophage-like phenotype. The crosstalk pathway described here specifically highlights a paracrine communication network, Byon et al. demonstrate that osteogenic VSMCs actively secrete soluble RANKL and chemokines to recruit and differentiate circulating monocytes by co-culture and migration assays [108, 109]. However, whether OLCs originate from VSMCs acquiring a macrophage-like phenotype ($Myh11^{+}LGALS3^{+}$ macrophage-like cells) remains to be delineated by using lineage-tracing models such as Myh11-Cre; Rosa-tdTomato in future studies.

Although AAA dilation is predominantly characterized by OLCs–mediated catabolism, the osteoblast-like VSMCs that drive anabolic calcification can simultaneously upregulate RANKL ligands to promote OLCs differentiation and enhance their catabolic activity [108, 109]. This seemingly paradoxical crosstalk raises a critical pathogenic question: Does the burst in microcalcification metabolic activity precede widespread, proteolysis–driven pathological expansion? Longitudinal *in vivo* imaging techniques, such as dual-tracer serial micro-PET/CT with ^{18}F-NaF (to detect calcification activity) and ^{18}F-FDG (to detect inflammation), offer the opportunity to dynamically monitor the entire process of calcification initiation, expansion, and rupture in AngII-induced AAA mice [110]. Simultaneously, detection of serum elastin degradation products (e.g., ELN peptides) and calcification-related factors (e.g., RUNX2, OPN) [111] will help establish a time-series correlation of imaging signals - molecular biomarkers - pathological phenotypes. Investigating this early microcalcification phase may therefore help elucidate the upstream initiating pathways that drive eventual aneurysmal expansion. Such an approach could identify more precise regulatory molecules or cellular targets for therapeutic intervention, with the ultimate aim of delaying AAA progression.

However, current animal models, particularly the AngII-induced $ApoE^{(-/-)}$ mouse, have elucidated the possible mechanisms of microcalcification, while representing acute, inflammation-driven aneurysm formation that occurs over weeks. In contrast, human AAA is characterized by chronic vascular aging-associated degeneration and is modulated by life-modifiable factors. Crucially, while mice mimic early active microcalcification, they rarely develop the extensive complex macrocalcification patterns seen in patients. This discrepancy limits their predictive value for late-stage biomechanical stability, though the mice's findings primarily reflect the early anabolic phase of osteogenic VSMCs transition. Therefore, future mechanistic studies need to be validated in more advanced animal models, such as co-infusion induced models or human organoids.

5. The Effects of Vascular Aging, Sex Differences and Metabolic Disorders on VC and AAA

5.1. Vascular Aging predisposing to VC and AAA formation

VC is increasingly viewed not just as a degenerative process, but as a hallmark of vascular aging [7]. Cellular senescence has also been found to contribute to the loss of repair capacity in the aortic wall, predisposing to aneurysm formation [112, 113]. While it is acknowledged that VSMCs' plasticity plays a fundamental role in aneurysm wall remodeling, loss of contractile function and gain of the synthetic phenotype are two key markers that resemble the aging process, including reduced proliferative capacity and a senescence-associated secretory phenotype (SASP). Aging VSMCs have been shown to accelerate the transdifferentiation process and decrease self-repair ability; more importantly, they exhibit a SASP phenotype, secreting pro-inflammatory cytokines and MMPs, and can even calcify under certain circumstances [112, 114].

Sirtuin 1 (SIRT1), a member of the nicotinamide adenine dinucleotide-dependent histone deacetylase family, plays a pivotal role in regulating aging and age-associated pathologies. It has been observed that reduced SIRT1 expression in senescent human VSMCs [115], and more importantly, that VSMCs-specific SIRT1 knockout mice have been shown to accelerate AngII-induced AAA formation, and increase the risk of rupture [116]. However, overexpression of SIRT1 in mice protects against aneurysmal degeneration [116]. Another distinct hallmark of vascular senescence is the progressive accumulation of DNA damage coupled with a compromised DNA repair capacity. This genomic instability, exacerbated by oxidative stress and VSMCs apoptosis, precipitates the early structural disintegration of the aortic wall. Crucially, oxidative stress plays a pivotal role in both VC and AAA progression, beyond its established function as a universal driver of calcification via phosphate imbalance and inflammatory signaling. The generation of ROS is intrinsically linked to the regulation of specific ECM-remodeling enzymes, such as MMPs and LOX, as well as the transition of VSMCs phenotype [96, 117].

Within the aneurysmal wall, upregulated ROS generation is concomitant with diminished mitochondrial biogenesis and activation of endoplasmic reticulum (ER)

stress pathways, specifically involving CHOP and activating transcription factor 6 (ATF6) signaling [118]. Evidence suggests that this pathological cascade is triggered by the accumulation of oxysterols, such as 7-ketocholesterol (7-KC), and 7-KC is involved in AngII-induced AAA progression by synergistically promoting MMP-2 expression and VSMCs apoptosis [119]. Therefore, maintaining organelle homeostasis may be a promising early therapeutic target for vascular aging. Mitochondrial dysfunction can further exacerbate ER protein folding imbalance and activate the unfolded protein response (UPR) pathway [120]. Moreover, the mitochondria-targeted antioxidant peptide SS31, can effectively reduce AAA incidence and severity by inhibiting the deleterious crosstalk between mitochondrial dysfunction and ER stress, thereby dampening inflammatory infiltration and suppressing MMPs expression [120].

In summary, vascular aging is a fundamental background for AAA pathogenesis; it induces aortic dilation through VSMCs apoptosis, osteogenic transition, and oxidative stress. The epidemiological predominance of AAA in the elderly population further corroborates the pivotal role of aging in the etiology of aortic dilative diseases. VC is recognized as a pathological hallmark of senescent vessels; it does not merely reflect a compensatory reparative response to senescence-induced injury, but also unveils a novel therapeutic perspective for targeting vascular aging and anabolic metabolism that precedes destructive dilation in aneurysm disease.

5.2. Sex-specific differences in VC and AAA

Although most aneurysms are more common in men, females present a higher risk of rupture and poor prognosis after EVAR or open repair [121]. Influenced by anatomical and biomechanical differences between sexes, women tend to present lower aortic wall strength and are more sensitive to smoking, which may contribute to rapid severity in AAA progression [122]. Given the protective role of estrogen by reducing inflammation and oxidative stress, women are less prone to develop AAA at the same age as men; however, the mechanistic evidence of hormonal effects on AAA progression is inconclusive. Moreover, sex differences extend to the contradictory findings regarding VC burden. Studies have reported that females exhibit a significantly higher mean calcification percentage and a higher iliac artery calcification score than males [123, 124]. This indicates a more complex AAA anatomy in women, which can also complicate femoral access during EVAR. A contrasting retrospective study utilizing fully automated volume segmentation found no statistically significant sex-based difference in total calcification volume, yet suggested that women present with more complex AAA anatomy than men [125]. Women generally have smaller aortic diameters, using relative calcification indices (such as normalized to body surface area) offers a more accurate comparison than absolute volume. Given that women often face a higher risk of AAA rupture, compared to men with the same aortic diameter, and considering the influence of estrogen fluctuations between pre- and post-menopausal status, it is necessary to establish sex-stratified imaging thresholds—such as macrocalcification on CT or active microcalcification detected by ^{18}F-NaF PET/CT—and to identify biomarkers indicative of active metabolic processes. These approaches would optimize risk stratification and prognosis in women with AAA.

Lutsey et al. identified a sex-modifying effect on the association between serum calcium levels and AAA risk, where elevated serum calcium levels were independently associated with an increased risk of incident AAA, specifically in women [126]. Furthermore, impaired renal function is a strong driver of arterial calcification. Compared to males of the same age, females, particularly elderly females, exhibit a higher prevalence of CKD stages 3-5 or unrecognized renal insufficiency [127]. Therefore, the elevated calcification burden observed in female AAA patients may be partially confounded by concomitant renal impairment, rather than driven solely by biological sex. Future sex-based AAA studies require multivariate adjustment for renal function and anatomical differences, to isolate the true biological impact of sex on AAA calcification.

5.3. Metabolic Disorders complicate VC and AAA

In contrast to the intimal calcification characteristic of atherosclerosis, medial calcification of the aorta, or Mönckeberg's sclerosis, is more closely associated with metabolic disorders such as aging, CKD, and DM [13]. In CKD, imbalanced calcium-phosphate metabolism and subsequent ectopic calcification are key factors that induce osteogenic differentiation of VSMCs and exacerbate systemic inflammatory responses [30]. Severe iliac artery calcification in AAA patients undergoing peritoneal dialysis may also influence subsequent clinical decisions regarding the feasibility of EVAR [128]. Diabetes patients often present with medial arterial calcinosis, and previously several clinical studies observed a protective effect of diabetes on AAA formation and progression [31]; whether calcification plays a role in inhibiting subsequent AAA progression among diabetes patients lacks clinical observations. Current advancements have shifted the protective role of diabetes itself to anti-diabetic therapies like metformin. Previous observations suggested that diabetic patients who were prescribed metformin showed promising

signals of reducing the growth rate of AAA and adverse events [129, 130]. The MetAAA trial showed no significant difference in aneurysm growth at 1-year follow-up [131]. However, the study was underpowered due to recruitment challenges during the COVID-19 pandemic [131]. Future ongoing clinical trials with larger non-diabetic cohorts are needed to verify the longer efficacy of metformin [132]. Mechanistically, studies indicate that metformin not only improves glycemic control but also exerts protective effects by mitigating oxidative stress and inhibiting vascular aging [129]. Research also found that metformin could inhibit VIC calcification by activating the PI3K/AKT signaling pathway [133] and identified that metformin is negatively associated with coronary artery calcification score in DM [134], suggesting that metformin affects VC.

Additionally, several experimental studies have shown that under conditions of hyperglycemia and elevated oxidative stress, advanced glycation end products (AGEs) promote osteogenic differentiation of VSMCs and VC. This process is mediated by the receptor for AGEs (RAGEs) via activation of mitogen-activated protein kinases (MAPK) and nuclear factor κB (NF-κB) signaling pathways [135, 136]. However, despite the complicated association between VC and AAA, the phenomenon of diabetes-mediating arterial calcification in AAA may offer new insights for further exploration.

Collectively, these findings highlight the complex regulatory roles of metabolic factors—including calcium-phosphate homeostasis, glycemic control, and oxidative balance—in the pathogenesis of VC.

6. Conclusions and Perspectives for Future Research

Current evidence elucidates the multifaceted role of VC in AAA pathogenesis. *In vitro* histological and biomechanical investigations have revealed that microcalcification deposition is closely associated with elastin degradation, while clinical observations predominantly associate macrocalcification with advanced stages of AAA. Based on these findings, we therefore propose a 'three-stage hypothesis' characterized by a non-linear relationship between calcification-related metabolic turnover (anabolism and catabolism) and AAA progression, as illustrated in Figure 2; however, the precise temporal chronology warrants further validation through single-cell RNA sequencing of calcific aneurysm tissue, and spatial transcriptomics. Current biomechanical perspectives indicate that the mechanical interface failure between active calcifications and the surrounding fibrotic tissue may precipitate the sudden rupture of AAAs. However, established inert macrocalcification may shield the aneurysmal sac by reducing global wall stress to a certain extent.

Continuous advancements in imaging technology constitute an indispensable foundation for the investigation of VC. Significant progress in detection, particularly through the application of AI for automated calcification segmentation and quantification, as well as the use of ^{18}F-NaF PET/CT, now enables a more comprehensive and dynamic evaluation in clinical practice. Importantly, the advantages of micro-CT, as well as NIRF and LSFM applied in animal models, enable sophisticated mechanistic research on early active anabolic calcific deposits, as serial micro-CT allows longitudinal detection of microcalcification and elastin degradation.

Clinically, calcification burden exhibits a dual association with AAA. It is positively correlated with accelerated expansion and rupture risk, yet paradoxically, circumferential patterns have been linked to reduced aneurysm expansion rates in specific contexts. FEA has elucidated this biomechanical duality, revealing that calcific deposits can concentrate stress at the interface with the vessel matrix while also potentially contributing to global wall stabilization under specific conditions. At the molecular level, key regulators such as RUNX2 and KLF4, which play important roles in the osteogenic transition of VSMCs and RANKL-mediated osteoclast-like differentiation of macrophages, represent promising therapeutic targets for modulating phenotypic plasticity in AAA. Furthermore, as aging accelerates the burden of vascular oxidative stress, modulating factors including hormonal influences and metabolic disorders, are integral to the pathological framework, underscoring the complexity of calcification in determining AAA progression and stability. Future research should focus on developing advanced dynamic imaging technologies capable of longitudinally tracking microcalcification activity and spatial heterogeneity, thereby moving beyond static burden assessments via multimodal fusion and AI-enhanced predictive modeling.

The specific spatial distribution of calcification is of critical value for the preoperative planning of EVAR [137, 138]. However, neither the Agatston score nor ^{18}F-NaF PET/CT assessment has currently been clinically integrated into routine AAA risk stratification; this may be constrained by its complexity, feasibility, and associated economic burden. Despite increasing evidence suggesting that risk prediction models incorporating calcification parameters outperform those relying solely on aneurysm diameter [20, 25, 26, 139], further comprehensive research is warranted to validate their prognostic value in clinical practice.

Despite advances in surgical repair, pharmacological management of AAA remains an unmet medical need. Statin represents a cornerstone therapy for reducing cardiovascular risk in AAA patients. In addition to its

lipid-lowering capacity, the pleiotropic anti-inflammatory effects of statin are well established and improve all-cause survival post-EVAR [129]. However, their efficacy in limiting aneurysm expansion remains equivocal [129]. Conversely, observational studies linking statin use to increased calcification density imply that this effect may stem from statin-induced inhibition of vitamin K2 synthesis [140, 141]. Vitamin K2 is an essential cofactor for the activation of an endogenous inhibitor of VC named matrix Gla-protein (MGP). Research has found that AAA patients in the highest tertile level of plasma MGP degradative products are associated with increased mortality risk, compared with first tertile for AAA cases, suggesting that vitamin K2 supplementation is likely not only beneficial for protecting against VC, but may also lower the risk of AAA-related adverse events by promoting MGP activity [12, 142]. However, no clinical trial has directly investigated the association between vitamin K2 supplementation and the incidence, progression, or prognosis of AAA. Notably, a randomized controlled trial reported that vitamin K2 supplementation over a two-year period did not lead to a statistically significant improvement in the progression or prognosis of aortic valve calcification [143]. Vlasschaert et al. further noted that vitamin K supplementation increases MGP carboxylation levels; however, its role in mitigating VC remains uncertain [144]. Thus, the direct association between vitamin K2 supplementation and AAA progression or prognosis warrants further clinical and mechanistic investigation.

Bisphosphonates, as potent inhibitors of osteoclastic function, can target macrophage-driven OLCs activity and mineral resorption. Previous studies have demonstrated that bisphosphonates can attenuate AngII-induced AAA formation [29, 145]. However, Nakahara et al. observed that risedronate treatment in AAA mice, while effectively reducing calcification activity and volume, paradoxically increased the final AAA diameter [25]. The authors postulated a temporal duality in its mechanism: though bisphosphonates may limit initial aortic expansion via early anti-inflammatory effects, their inhibition of macrocalcification formation might ultimately compromise mechanical stability, thus contributing to late-stage expansion [25]. Although preclinical studies showed potential protective effect, its clinical efficacy in AAA patients remains inconclusive. A recent systematic review found that bisphosphonates treatment had no effect on future cardiovascular events [146]. Therefore, whether it can be a further promising therapeutic strategy for AAA remains a subject of ongoing uncertainty. Additionally, a monoclonal antibody, denosumab, also targets catabolism in VC via the RANKL pathway, potentially inhibiting aortic wall degeneration. While its efficacy has been investigated in the context of aortic stenosis and other cardiovascular diseases [147, 148], its specific therapeutic efficacy in AAA remains to be elucidated [40].

In addition to the aforementioned drugs in AAA therapy, as recently reviewed by Puertas-Umbert, some promising therapeutic research targeting ROS and ECM stabilization is emerging [129]. As traditional anti-inflammatory and anti-hypertensive drugs have shown limited efficacy in halting aneurysm growth, this necessitates a paradigm shift towards targeting specific structural and metabolic drivers, such as VC and its upstream regulators.

Although Li et al. found that additional HA application exacerbates AngII-induced AAA formation in an animal model [25], it remains unclear whether targeting VC halts or delays AAA progression. Given the non-linear dynamics between microcalcification and AAA progression, we hypothesize that the timing of intervention and concurrent ECM preservation likely determine the outcome. While extensive macrocalcification may act as a protective shell that bears the global stress in the advanced AAA stage, it is more beneficial to focus on the anabolic burst of microcalcification, as well as the catabolic elastin degradation in the early phase. Hossack et al. further confirmed that ruptured AAAs exhibit greater micromechanical heterogeneity, as assessed by nanoindentation and micro-biomechanical experiments, in which microcalcification is positively associated with stiffness mismatch [149].

Emerging nanomedicine platforms offer a precise therapeutic approach to address the complex microenvironment of AAA. Recent studies utilizing nanoparticles with ROS-responsive properties [150] and multi-target synergistic therapies have demonstrated the feasibility of simultaneously suppressing inflammation, stabilizing ECM, and inhibiting VC in animal models [151, 152]. Nosoudi et al. demonstrated that nanoparticles loaded with calcium chelator EDTA and an elastin-stabilizer polyphenol pentagalloyl glucose (PGG) can simultaneously remove pathological VC deposits and restore matrix integrity, thus suppressing aneurysm growth in a rat model [153]. By removing rigid mineral deposits while reinforcing the compliant elastin matrix, this dual-targeting strategy addresses the underlying stiffness mismatch and establishes a blueprint for future therapies aimed at VC.

Notably, these preclinical successes were demonstrated mainly in the calcium chloride-induced rat model. While this model robustly recapitulates the inflammatory and calcific features of AAA, the calcification process is partly driven by exogenous chemical induction. Therefore, future translational studies should validate these targeted therapies in metabolically

driven models, such as high-phosphate reinforcing AngII-induced AAA models [154], to confirm their efficacy against spontaneous anabolic calcification observed in human vascular pathology.

However, we propose that methodological heterogeneity (e.g., variations in CT protocols) is the primary technical confounder of the clinical paradox effect, whereas biological heterogeneity (e.g., differences in patient proportions with concomitant CKD or diabetes) dictates the intrinsic calcification pattern. Establishing standardized quantitative calcification protocols in future large-scale, prospective AAA clinical cohorts to correlate early metabolic changes in microcalcification with subsequent aneurysm growth will help exclude methodological heterogeneity, with stratified analysis to isolate the actual biological effect. Crucially, elucidating the fundamental micro-structural heterogeneity associated with calcification in stable and ruptured AAA pathology is essential. Complementing this in animal models with advanced preclinical imaging to track calcification dynamics during AAA progression across temporal and spatial scales will be vital for a comprehensive understanding, particularly for validating novel stage-specific therapies. Ultimately, individualized risk prediction and clinical management for AAA could be significantly enhanced by integrating conventional biomarkers with the morphological, metabolic, and biomechanical features of VC.

Data Availability

This manuscript constitutes a review paper, drawing all supporting evidence from publicly available research that is appropriately cited.

Authors'contributions

Kexin Zhao: Writing – original draft, Writing – review & editing. Weichang Zhang: Writing – review & editing. Chang Shu: Supervision, Project administration, Funding acquisition, Conceptualization, Writing – review & editing.

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Competing interests

The authors confirm the absence of any financial, commercial, or personal conflicts of interest affecting this research.

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