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Review

How does atherosclerotic plaque become calcified, and why?

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Abstract: Vascular calcification involves the crystallization of calcium/phosphate in the form of hydroxyapatoite in the extracellular matrix of the arterial wall. Vascular calcification is categorized into 3 main etiologies: (1) inflammatory/atherosclerotic (mostly intimal), (2) metabolic (mostly medial), and (3) genetic background (mostly medial). Several overlapping mechanisms trigger all three types of calcifications. Intimal coronary artery calcification simultaneously develops with the progression of atherosclerosis and has been recognized as a surrogate marker of atherosclerotic inflammatory vascular disease. Pathologically, atherosclerotic calcification initially occurs as microcalcifications (0.5 to 15 μm) and results in larger dense calcification, eventually forming sheet calcifications (>3 mm). Among the plaque types, the degree of calcification is the highest in fibrocalcific plaques, followed by healed plaque ruptures, and is the lowest in pathologic intimal thickening. Recent pathologic and imaging-based studies suggest that massive dense calcifications are usually associated with stable plaques, whereas microcalcifications are indicative of vulnerable plaques which may cause acute thrombotic events. Although the mechanisms of calcification are not fully elucidated, apoptotic inflammatory cells and smooth muscle cells, along with the induction of bone formation, play crucial roles in its initiation and progression. A deeper understanding of vascular calcification will improve the risk stratification and patient outcomes through the development of new therapies.

Keywords: atherosclerosis; pathology; coronary artery calcification; coronary artery disease; intravascular imaging

1. Introduction

Coronary calcification is a key indicator of advanced atherosclerosis. The earliest lesions to show calcification are pathologic intimal thickenings, which contain extracellular lipid pools and proteoglycan matrices with microcalcifications ranging from 15 μm to 1 mm, fragmented calcifications over 1 mm, and sheet-like calcifications over 3 mm. Maximum calcifications are found in fibrocalcific plaques and healed plaque ruptures, which are detectable by either computed tomography or intravascular imaging. Lesions with acute thrombi, such as plaque ruptures and erosions, have less calcification, which often cause acute coronary syndromes. Calcified nodules, which are the least common cause of acute thrombosis, develop in highly calcified lesions and may form around fibrocalcific plaques. This review offers a comprehensive understanding of coronary artery calcifications from a pathological perspective.

2. Pathology of coronary artery calcification

Arterial wall calcifications are categorized into three main types: (1) inflammatory (atherosclerotic, mostly intimal), (2) metabolic (chronic kidney disease [CKD] and diabetes mellitus [DM], affecting both intimal and medial, also known as Monckeberg's calcification), and (3) genetic causes [1]. Atherosclerotic intimal calcifications are distinct from medial calcifications, though overlapping factors can contribute to both. While medial calcifications are generally unaffected by lipid deposition or inflammation, intimal calcification typically are. Both types may coexist in the same vessel due to risk factors such as DM, hypercholesterolemia, and CKD. Medial calcifications often result from the transformation of smooth muscle cells into osteochondrogenic cells, which is driven by ossification biomarkers and osteoblastic differentiation factors [2]. Genetic disorders can also influence metabolic mediators, thereby causing both medial and intimal calcifications. Despite these classifications, there is considerable overlap between the mechanisms.

2.1. Definitions of different types of calcification by histology

Calcifications are classified by the plaque size and type [3,4] (Figures 1 and 2). A microcalcification is the earliest form, and it consists of calcium particles that range from ≥0.5 μm to <15 μm in diameter. A punctate calcification ranges from >15 μm to <1 mm and is associated with macrophage apoptosis at the necrotic core's outer rim. The mechanisms of fragmented calcification, which is ≥1 mm in size, are poorly understood. A sheet calcification involves greater than one quadrant of the vessel, thereby affecting smooth muscle cells and the collagen matrix, independent of the necrotic core. A nodular calcification results from the fragmentation of a sheet calcification and is surrounded by fibrin, which does not protrude into the lumen. When such a calcification protrudes into the lumen and forms a calcified nodule, which is often accompanied by a luminal thrombus. It is rare that a bone formation with a trabeculae and a marrow space appears in severely calcified arterial segments, indicating a link between osteogenesis and severe arterial calcifications.

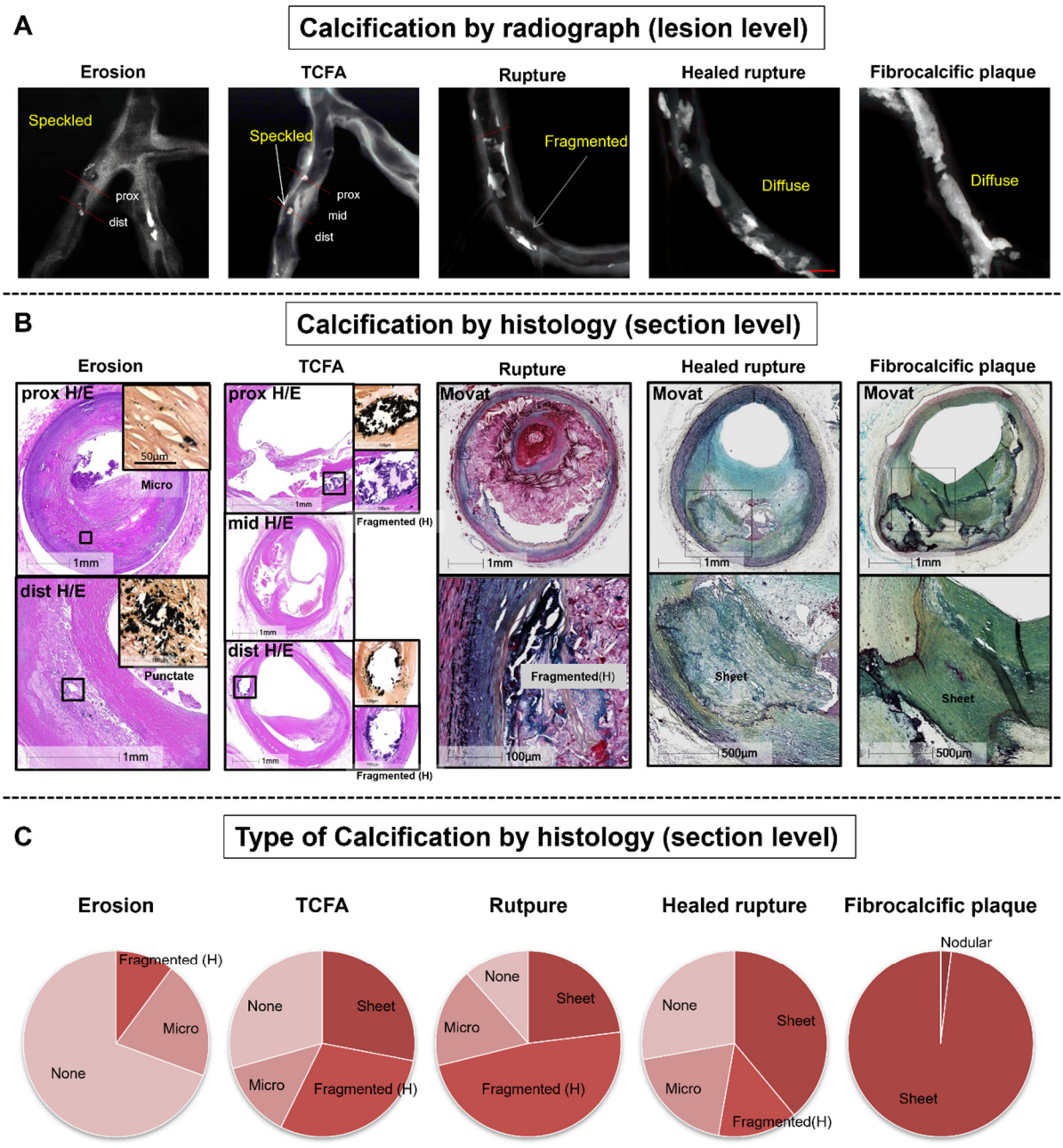

Figure 1. Type of calcification by radiography and histology. (A) The typical patterns of calcification by radiography for each plaque type. (B) Corresponding histology with low- and high-power images of sections taken from the areas shown in radiographs with red lines. The scale bar (white line) in the radiograph indicates magnification. A microcalcification by histology is invisible by radiograph in the proximal section from a case of coronary erosion. A speckled calcification by a radiograph corresponds to either a punctate or fragmented calcification by histology. Thin fibrous cap fibroatheroma (TCFA) lesions shows 3 sites of sectioning and 2 spots (proximal and distal) of speckled calcium,

with the middle section showing TCFA without calcification. A plaque rupture site shows a fragmented calcification by radiograph, which corresponds to a fragmented calcification by histology. Healed rupture and fibrocalcific plaques sites both show diffuse calcifications by radiographs, which correspond to sheet calcifications by histology. (C) Types of calcifications by histology (section level) in different types of plaques. Reproduced with permission from Mori et al. [3]. Abbreviations: Dist: Distal; Fragmented (H): Fragmented by histology; H/E: Hematoxylin-eosin stain; Mid: Middle; Prox: Proximal; TCFA: Thin-cap fibroatheroma.

2.2. Progression of atherosclerosis and calcification

2.2.1. Progressive atherosclerotic lesion

Atherosclerosis involves a dynamic process in which early lesions progress to advanced stages complicated by acute luminal thrombosis (Figure 3). Non-atherosclerotic intimal lesions, such as adaptive intimal thickening (AIT) and diffuse intimal thickening (AHA Type I), exist from birth and are common in atherosclerosis-prone regions. AIT, which is a physiological response to blood flow, can transition into pathologic intimal thickening (PIT) in high-risk areas [5]. Fatty streaks (FS) or intimal xanthomas (AHA Type II) are early lesions mainly composed of macrophage foam cells and lipid-laden smooth muscle cells (SMCs). These early lesions normally lack calcifications. PIT (AHA Type III) is recognized as the earliest lesion of progressive atherosclerosis. PIT contains remnants of SMC within an ECM that consist of proteoglycans and collagen (Type III) with a co-existing lipid pool [6]. This lipid pool is distinctly different from the necrotic core (NC) seen in fibroatheroma (FA), which is characterized by acellular debris and a lack of an ECM. The lipid pool formation marks the initial stage of NC development, driven by macrophage recruitment, increased metalloproteinase activity, and macrophage apoptosis. Calcifications in PIT first appear as microcalcifications within lipid pools [4], primarily due to SMC apoptosis [7–9], with contributions from macrophage-derived matrix vesicles [10]. SMC apoptosis produces fine microcalcifications, while apoptotic macrophages yield larger, punctate calcifications. Typically, the calcification is located in the intima near the internal elastic lamina. Microcalcifications are observed in 57% of PIT [11], and these calcifications coexist with bone-related proteins such as osteoprotegerin (OPG), osteopontin (OPN), and matrix Gla protein (MGP) (Figure 2A–B). FA, which is a progressive stage of atherosclerosis (AHA Type IV), features an acellular NC formed through macrophage infiltration into lipid pools [12]. Early FAs show macrophage infiltration, localized ECM loss, and free cholesterol concentration, with proteoglycans and Type III collagen remaining present. Late-stage FAs have increased free cholesterol, cellular debris, and complete ECM depletion due to degradation by matrix metalloproteinases from macrophages and SMCs. Numerous apoptotic macrophages contribute to a high presence of apoptotic bodies within the NC. Early FAs exhibit either microcalcifications or punctate calcifications [11], which coalesce into larger aggregates over time, thus progressing outward from the NC into the collagenous matrix that surrounds it. An intraplaque hemorrhage from compromised vasa vasorum near the NC can cause significant luminal narrowing. As the plaques progress, a thick fibrous cap composed of Type I and III collagen, proteoglycans, and interspersed SMCs with an endothelial layer forms over the NC. If the cap is thin (under 65 μm) [13], it is termed a thin fibrous cap fibroatheroma (TCFA), also called a "vulnerable plaque," which is prone to rupture and potential luminal thrombus

formation. The vulnerability of a plaque is determined by the fibrous cap thickness, primarily composed of Type I collagen and infiltrated by macrophages and T lymphocytes [14–16]. The majority of TCFA and ruptured plaques are localized in the proximal left anterior descending coronary artery and left circumflex artery, and are more uniformly distributed in the right coronary artery. In 92% of cases, these lesions clustered within 2 or fewer nonoverlapping 20 mm segments [17]. Vessel-specific hemodynamic conditions likely contribute to plaque progression. However, an understanding of the exact factors that determine whether a lesion progresses to stenosis remains incomplete.

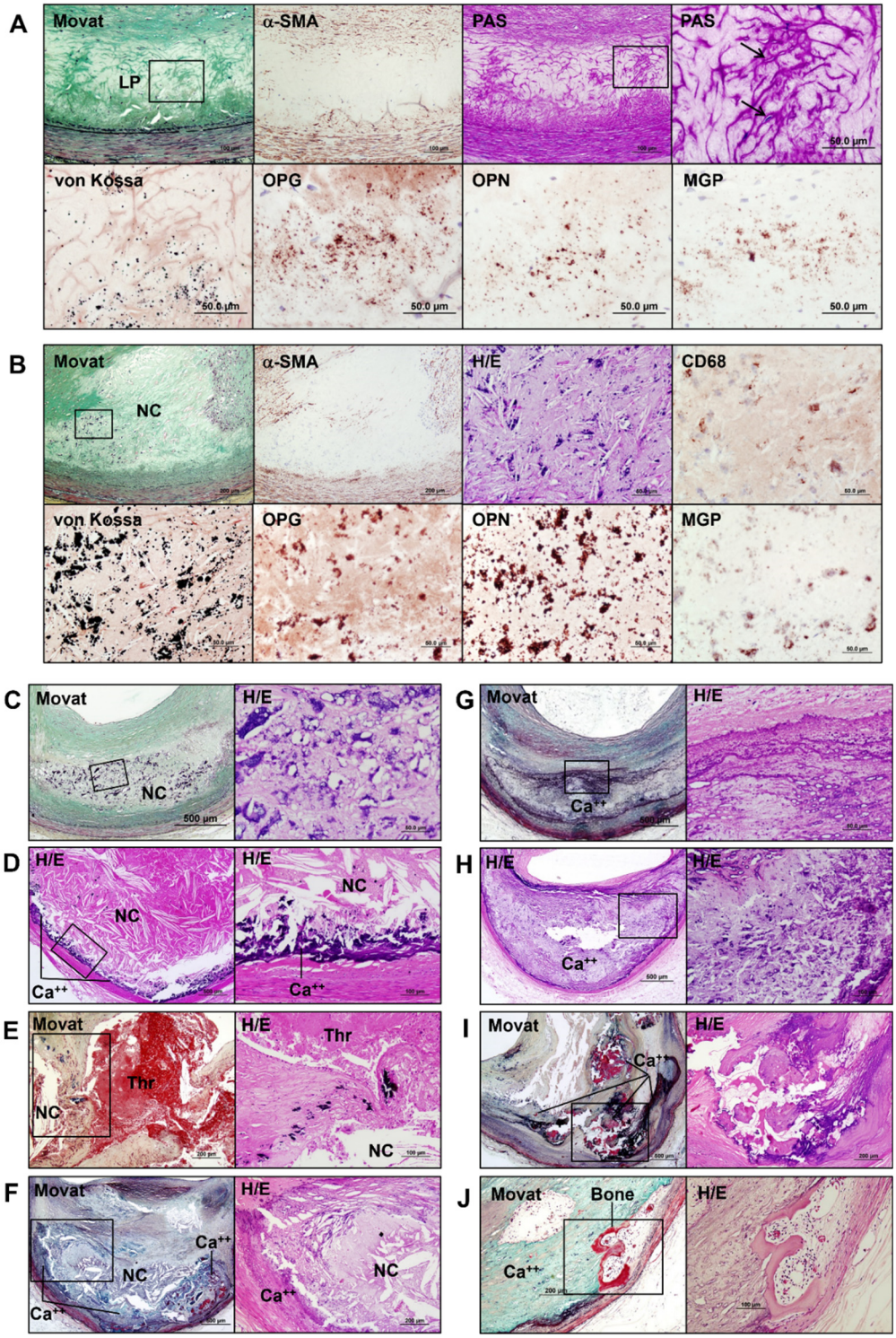

Figure 2. Histologic progression of coronary calcifications. Non-decalcified arterial segments (A and B) and decalcified segments (C–J) were serially sectioned for microscopic assessment. A) Pathologic intimal thickening (PIT) characterized by a lipid pool (LP) that lacks smooth muscle cells (SMCs; negative for α-smooth muscle actin [α-SMA]) and the presence of apoptotic SMCs, which can be identified by prominent basement membranes, which stain positive with periodic acid–Schiff (PAS), and the arrows point to in the high-power image (top right corner). An early microcalcification (≥0.5 μm, typically <15 μm in diameter) likely results from SMC apoptosis, and a calcification is detected by von Kossa within the LP (corresponding with a boxed area in the Movat image), where bone-related proteins such as osteoprotegerin (OPG), osteopontin (OPN), and matrix Gla protein (MGP) are detected. B) Early fibroatheroma not only lacks SMCs but is also infiltrated by macrophages, which eventually undergo apoptosis and calcification, which is observed as punctate (≥15 μm) areas of calcification. The microcalcification in the early necrotic core (NC) shows variable amounts of staining for the macrophage CD68 antigen; however, von Kossa staining clearly shows relatively larger punctate areas of calcification which resulted from macrophage cell death within the NC as compared with the microcalcification of dying SMCs. These calcified macrophages show the colocalization of bone-related proteins. A substantial amount of macrophage calcification can be observed in early NC (C); however, the degree of calcification in NC typically increases toward the medial wall, where fragmented calcifications can be seen (D). Additionally, microcalcifications that result from either macrophages or SMC deaths can be detected within a thin fibrous cap and may be associated with a plaque rupture (E). A calcification generally progresses into the surrounding area of the NC (F), which leads to the development of sheets of calcification, where both the collagen matrix (G) and the NC itself are calcified (H). A nodular calcification may occur within the plaque in the absence of a luminal thrombus and is characterized by breaks in calcified plates with fragments of calcium separated by fibrin (I). An ossification may occur at the edge of an area of calcification, especially in a nodular calcification (J). Reproduced with permission from Otsuka et al. [4]. Abbreviations: Ca^{++}: Calcification, H/E: Hematoxylin and eosin; LP: Lipid pool; MGP: Matrix Gla protein; NC: Necrotic core; OPG: Osteoprotegerin; OPN: Osteopontin; PAS: Periodic acid–Schiff; SMA: Smooth muscle cell actin; Thr: Thrombus.

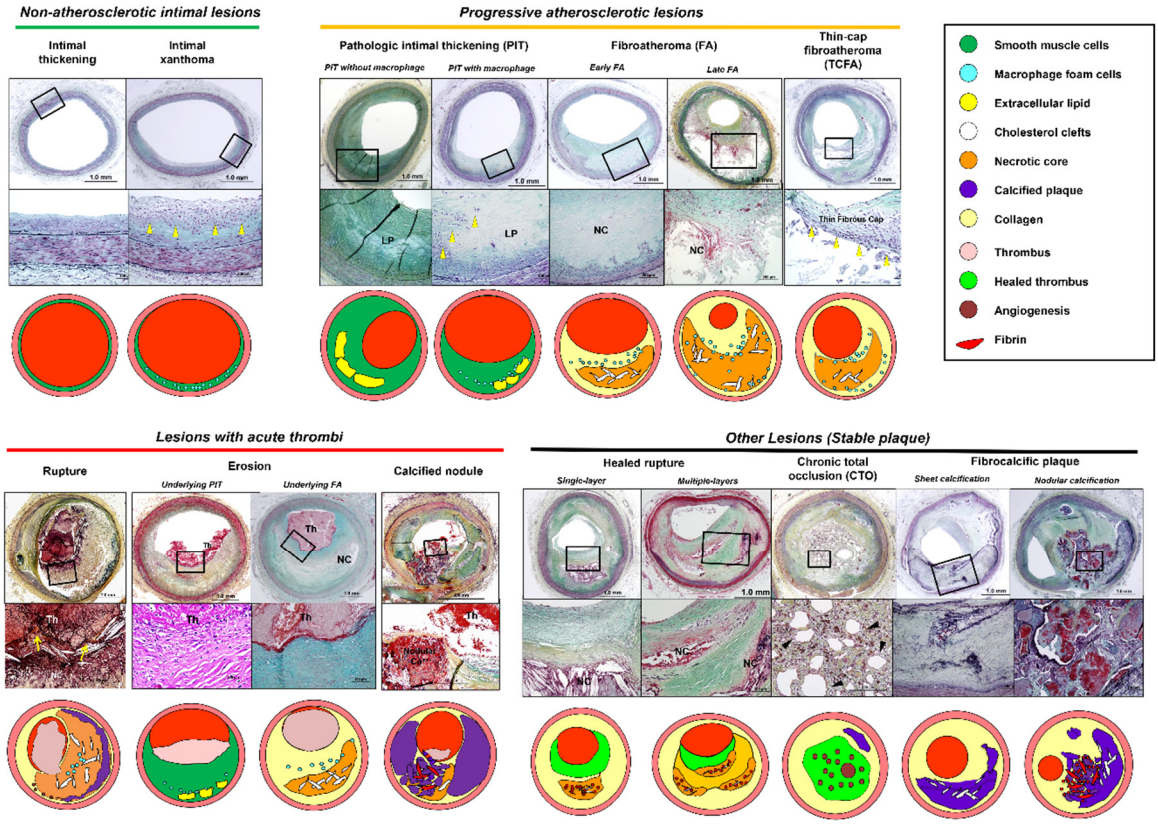

Figure 3. Spectrum of human atherosclerosis progression. The two non-progressive lesions are adaptive intimal thickening (AHA Type I) and intimal xanthomas (foam cell collections know as fatty streaks, AHA Type II). Pathological intimal thickening (PIT, AHA Type III, transitional lesions) marks the first of the progressive plaques since they are the assumed precursor to more advanced fibroatheroma (FA), which are classified into early and late FAs. A thin-cap fibroatheroma (TCFA) is a precursor lesion of a plaque rupture. Lesions with acute thrombosis are rupture, erosions (occur on a substrate of PIT or FA), and calcified nodules. Other lesions include healed plaque ruptures (single-layer or multiple-layers), chronic total occlusions, and fibrocalcific plaques (usually with calcified sheets). Modified and reproduced with permission from Yahagi et al. [12]. Abbreviations: LP: Lipid pool; NC: Necrotic core; Th: Thrombus.

2.2.2. Coronary thrombosis

A plaque rupture (PR) is the leading cause of acute coronary syndrome (ACS), which accounts for 65% of luminal thrombosis [6]. Compared to TCFA, ruptured plaques have a larger NC and more inflammatory cells in the fibrous cap. Rupture typically occurs at the thinnest, weakest region of the fibrous cap. Factors such as a high macrophage density, proteases, and a high shear and tensile stress weaken the cap at the rupture site [18,19]. Additionally, microcalcifications from macrophages or SMCs within a thin fibrous cap may trigger rupture [20]. When the cap ruptures, circulating blood contacts highly thrombogenic components within the NC, thus resulting in luminal thrombus formation.

The second most prevalent cause of ACS (25 to 30%) is plaque erosion, which occurs in the absence of a rupture, where luminal thrombi are in direct contact with a denuded intimal surface composed of SMCs and a proteoglycan matrix [21]. The underlying lesion of eroion is typically less advanced than in ruptured plaques, and usually exhibit the characteristics of early lesions (mostly PIT or early FA) without an extensive NC, hemorrhage, or calcification. Plenty of SMCs and proteoglycans such as versican, hyaluronan, and Type III collagen are observed near the thrombus attachment site of erosion, which are different from ruptured or stable plaques, with the latter being rich in biglycan, decorin, and Type I collagen [22]. Erosion is frequently observed at arterial bifurcations and has been linked to shear stress, endothelial cell dysfunction, and factors such as myeloperoxidaze, neutrophil extracellular traps, and hyaluronan. However, the detailed mechanisms by which erosion occurs remain poorly understood.

Calcified nodules are the least frequent (<5%) cause of ACS [6], primarily occurring in highly calcified, tortuous arteries. Pathologically, breaks in calcified fibroatheromas may form protruding fragmented nodules, thus disrupting the cap and endothelium and leading to a luminal, platelet-rich thrombus [23]. These eccentric nodules often contain fibrin intermingled with calcium spicules, which are occasionally accompanied by osteoclasts and inflammatory cells. More common in older adults and patients with tortuous arteries, diabetes mellitus, or chronic kidney disease, these lesions typically appear at points of maximum artery tortuosity such as the mid-right coronary artery or near bifurcations of the left main While similar and more prevalent, a nodular calcification involves an intact fibrous cap, with the calcified nodules staying within the arterial intima, sometimes causing medial disruption and adventitial protrusion.

2.2.3. Healed plaque and ficrocalcific plaque

Further progression of calcification leads to calcified plaques with sheets or plates (>1 quadrant), and often involve SMCs and a collagenous matrix, regardless of the necrotic core. Healed plaque ruptures are detected in severely narrowed arteries, thereby showing breaks in the Type I collagen-rich fibrous cap with an overlying plaque rich in SMCs and surrounded by proteoglycans or Type III/Type I collagen, depending on the healing phase [24]. Early-healed lesions are dominated by proteoglycans and Type III collagen, and are eventually replaced by Type I collagen. Cross-sectional luminal narrowing increases with more healed ruptures, thus contributing to stenosis progression [24]. Defined by thick fibrous caps and extensive calcification, fibrocalcific plaques are common in patients with a stable angina and severe luminal narrowing. Coronary calcification correlates with plaque burden, though not linearly with plaque instability—greater calcification often means more stable plaques. Fibrocalcific plaques usually have minimal or no NC and likely represent end-stage ruptured plaques, healed plaque ruptures, or fibroatheromas, which are all characterized by dominant calcification. However, there are no comprehensive, longitudinal studies that pathologically evaluate the progression or regression of these plaque characteristics.

3. Difference between coronary artery and carotid artery calcification

Atherosclerotic lesions in the carotid arteries share many characteristics with advanced coronary artery disease, thus allowing for the use of similar classifications. Based on our experience, most lesions from asymptomatic patients with carotid artery disease consist of fibrocalcific plaques.

Interestingly, the frequency of calcification in both coronary and carotid arteries is comparable, with maximum calcification in the carotid arteries occurring in lesions where the lumen is narrowed by more than 70% in the cross-sectional area. The incidence of non-thrombotic fibrocalcific plaques in the carotid arteries is 11% in stroke patients, 31.9% in those with TIAs, and 39.1% in asymptomatic patients [25]. A calcified nodule is more common in the carotid than in the coronary bed, and similarly appears to remain the least frequent cause of thrombosis, thereby accounting for 7.7 % of all carotid thrombi [25].

Coronary artery calcium (sheet calcification) is often found in significantly stenotic lesions (>75% cross-sectional area) rich in fibrous tissue, and is a significant independent predictor of future cardiac events [26]. However, the relationship between carotid calcification and cerebrovascular disease remains less clear. Some studies suggest that carotid plaque calcification may provide mechanical stability to the plaque, thus potentially serving as a protective feature. Conversely, other research indicates that the calcium within carotid plaques may be an independent marker for luminal stenosis and ischemic symptoms [27].

4. Evaluation of calcification using imaging devices

Intravascular imaging devices such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS), which are used during PCI, can detect coronary artery calcifications. OCT or optical frequency domain imaging (OFDI) can identify sheet calcifications as a signal-poor or heterogeneous region with a sharply delineated border [14]. The appearance of a nodular calcification is different from a sheet calcification. A nodular calcification, which follows a sheet calcification, presents a heterogeneous signal with high attenuation, presumably due to fibrin interposed between nodules (Figure 4). OCT/OFDI offers a higher spatial resolution compared to an IVUS; however, the penetration depth of the near-infrared light used in OCT/OFDI is approximately 2 mm, which is less than half of that of an IVUS. Therefore, while OCT/OFDI excels in observing the fine tissue characteristics on the surface of the vessel, it has limitations in visualizing the entire vessel and assessing remodeling. In particular, lipid components (necrotic core) and acute thrombus often cause significant attenuation of the OCT/OFDI signal due to light scattering, making it difficult to observe the areas behind them (Figure 4).

We have previously reported the utility of micro-computed tomography (micro-CT), which has a resolution at the micron-level range, to detect the morphologic features of atherosclerosis obtained during an autopsy [28,29]. Figure 5 shows that micro-CT allows for a more detailed observation of the plaque characteristics compared to CT, which is used in clinical practice, thus suggesting the possibility of obtaining images that are closer to the pathological findings [30]. With the improvements in CT imaging technologies, one day, identifying microcalcifications might become feasible during routine clinical practice, which are indicative of unstable plaques, as well as distinguishing between sheet calcifications and nodular calcifications in severe calcified lesions. Techniques such as spectral CT and advanced morphometric analysis may play a key role in achieving these capabilities [31,32]. Furthermore, it has been reported that a higher calcium density is inversely correlated with the risk of coronary artery disease [33,34]. The low calcium density is more likely associated with microcalcifications seen in unstable plaques, whereas a high calcium density may represent fibrocalcific plaques, which are indicative of a more stable plaque morphology. They could become

instrumental in stratifying high-risk patients, thereby enhancing the precision of cardiovascular risk management.

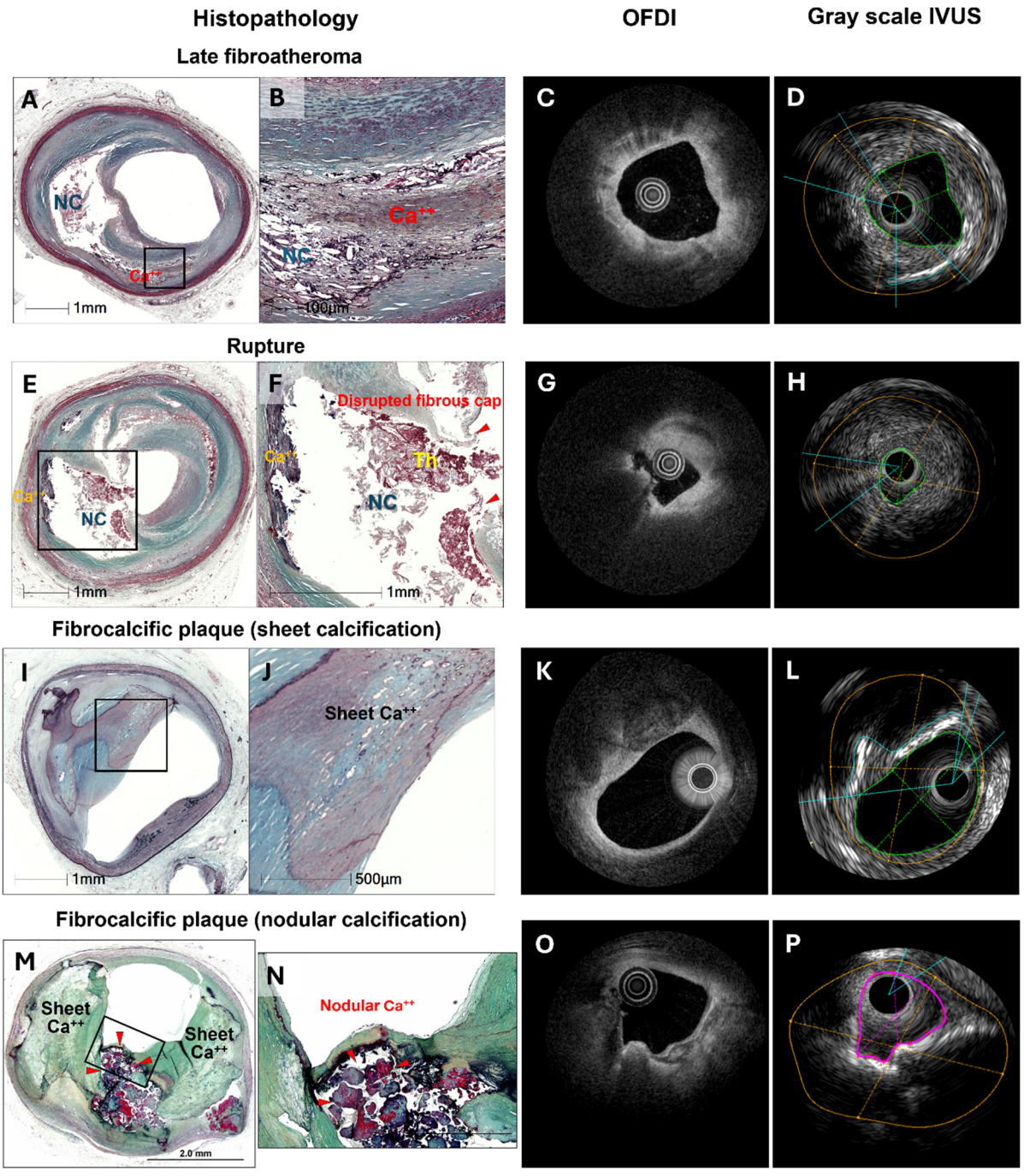

Figure 4. Co-registered images of pathological findings with OFDI and IVUS. Co-registered images of pathological findings with optical frequency domain imaging (OFDI) and intravascular ultrasound (IVUS). The left images show low-power magnifications, while the right images show high-power magnifications. Late fibroatheroma (A, B): Sheet calcification adjacent to the necrotic core is observed (A, B). OFDI shows a corresponding area of low signal attenuation at the necrotic core site (C). In IVUS, calcifications with

high-intensity acoustic shadowing are visible in the 5 to 6 o'clock direction (D). Rupture (E, F): At low-power image, sheet calcifications are seen at the outer rim of the necrotic core, while high-power images reveal a fibrous cap disruption and thrombus extending from the necrotic core. OCT and IVUS images (G, H) exhibit significant signal/echo attenuation due to the thrombus and necrotic core, thereby obscuring the deeper layers of the plaque. In such lesions, identifying calcifications at the outer rim of the necrotic core, which is common in fibroatheroma, may be undetectable with intravascular imaging. Fibrocalcific plaque (I, J): Sheet calcifications appear as a well-defined low-signal structure in OFDI and is easily identifiable in an IVUS (K, L; 9 to 1 o'clock direction). Nodular calcification (M, N): Nodular calcifications are observed between areas of sheet calcifications. In OCT, nodular calcifications appear as high-brightness areas with attenuation and poorly defined margins, unlike sheet calcifications (O). In an IVUS, the same region shows acoustic shadowing, thus indicating calcification; however, distinguishing between nodular and sheet calcifications may be difficult. Images A–D and M–P were modified and reproduced with permission from Mori et al. [3] and Nakano et al. [35]. Abbreviations: IVUS: Intravascular ultrasound; NC: Necrotic core; OFDI: Optical frequency domain imaging; Th: Thrombus.

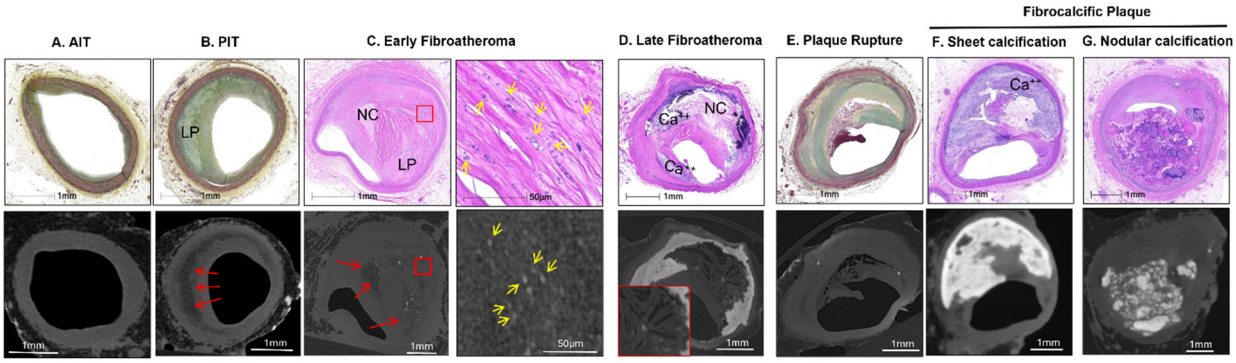

Figure 5. Micro-computed tomography (CT) images with corresponding histological sections showing the progression of atherosclerosis. Upper panels are histological images with corresponding micro-CT images below. (A) Adaptive intimal thickening (AIT). (B) Pathological intimal thickening (PIT) with lipid pool (LP); micro-CT image shows low density area (red arrows) corresponding to an LP. (C) Early fibroatheroma with a necrotic core (NC) and an LP, with corresponding low-density area (red arrows) in micro-CT. The right panel (top) histology from the red box in (C) and the corresponding micro-CT image show microcalcifications (yellow arrows). (D) Late fibroatheroma with NC, cholesterol clefts, and calcifications at the outer rim of the NC. Micro-CT image shows the presence of cholesterol clefts (highlighted red box) with calcifications. (E) Plaque rupture; histological image shows luminal thrombus and a disrupted fibrous cap with the underling necrotic core. Corresponding micro-CT image shows the same morphologies. (F) Fibrocalcific plaque, histological, and micro-CT images showing sheet calcium. (G) Nodular calcification; histological image shows nodules of calcification, which can be

clearly seen in the corresponding micro-CT image. Modified and reproduced with permission from Jinnnouchi et al. [30]. Abbreviations: Ca^{++}: Calcification; NC: Necrotic core.

5. Gender, coronary risk factors, statins, and calcification

5.1. Gender and coronary calcification

We previously reported pathological differences in the extent of coronary calcifications between the genders [36,37]. When stratified by decades, men exhibited greater calcifications than women up to their sixties, whereas the prevalence was similar in the seventies, thus suggesting a rapid calcification development during the postmenopausal period. Additionally, postmenopausal women have three times higher calcifications than premenopausal women. Regarding the etiology of ACS, rupture occurred in 64.7% (n = 178) and erosion in 34.5% (n = 95) of cases in men under 50 years old (n = 275), while rupture was seen in 76.6% (n = 118) and erosion in 16.9% of cases (n = 26) in men over 50 years old (n = 154) [38]. On the other hand, rupture occurred in 22.9% (n = 11) and erosion in 77.1% of cases (n = 37) in women under 50 years old (n = 48), whereas rupture was seen in 50% (n = 23) and erosion in 21.7% of cases (n = 10) in women over 50 years old (n = 46) [38]. Unlike men, young women predominantly experienced erosion; however, the incidence of rupture increased in women over 50 years old. The development of atherosclerosis differed between men and women, not only in the prevalence and impact of coronary risk factors, but also due to the presence of female-specific risk factors, which are gaining attention [39]. The coronary artery calcification score (CACs) evaluated by CT predicts the risk of cardiovascular events over a 10-year period in women in a graded fashion [40]. A study of 63215 asymptomatic individuals evaluated by CT showed that while women were less likely to have prevalent CACs than men at a given age, detectable CACs indicated a higher relative risk of cardiovascular disease in women [41]. An emerging risk marker for women is breast arterial calcification, which is a medial artery calcification incidentally found on mammograms, and are associated with CACs and future cardiovascular risk [42–44]. Detecting breast arterial calcifications might be a useful additional cardiovascular risk screening.

5.2. DM, CKD, and coronary calcification

DM and CKD are significant risk factors for coronary artery disease. Our autopsy registry showed that the mean percent plaque area composed of NC was greater in DM subjects compared to non-DM subjects. DM subjects had a higher mean percent calcified area than non-DM subjects (12.1% vs. 9.4%; P = 0.05) [45]. Higher HbA1c levels in sudden death cases were associated with fewer non-calcified lesions and more sheet calcifications [46]. Consistent with these morphometric findings, the number of healed plaque ruptures was the highest in the DM subjects, thus indicating more advanced atherosclerotic plaques. Individuals with CKD have a higher incidence and prevalence of CAC and rapid CAC progression compared to the general population [47,48]. A recent analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) study categorized 6780 subjects by the DM and CKD status, and showed that CACs predict cardiovascular disease onset in CKD patients, regardless of the DM presence [49]. Dysregulated mineral metabolism, including increased phosphate, fibroblast growth factor 23, parathyroid hormone, and 1,25-dihydroxy vitamin D, along with various local and systemic factors, contribute to cardiovascular calcification in CKD [50].

5.3. Statins and coronary calcification

The effect of a high-intensity statin therapy on plaque has been well established using imaging devices. Statins slow the progression of the overall coronary atherosclerosis volume, increase the plaque calcification, and reduce the high-risk plaque features. The PARADIGM clinical trial compared coronary plaque volume changes in statin-naive (n = 474) and statin-taking patients (n = 781) using CT [51]. Statin users showed a slower atheroma volume progression (1.76% vs. 2.04% per year, P = 0.002) but a faster CAC burden progression (1.27% vs. 0.98% per year, P < 0.001). New high-risk plaque features were lower in statin users (0.9% vs. 1.6% per year, P < 0.001). A recent cohort study of 857 patients (2458 lesions) assessed the association between statin use and atherosclerotic plaque progression using CT over more than two years [52]. The plaque compositions were categorized by the CT attenuation values: low attenuation, fibro-fatty, fibrous, low-density calcium, high-density calcium, and 1K plaques. Statin use reduced the low attenuation and fibro-fatty plaques but increased the high-density calcium and 1K plaques. In lesions without either a baseline low-attenuation or fibro-fatty plaque, statin therapy did not change the overall calcified plaque volume but promoted more dense calcium formation. These findings suggest that statins reduce the necrotic core and promote sheet calcifications.

6. Conclusions

Calcification is a critical finding in the progression of coronary atherosclerosis. It serves not only as a predictor of future cardiovascular events, but also as an indicator that can differentiate between unstable and stable plaques. With advancements in imaging technologies, it has become possible to identify coronary calcifications, thus leading to new insights into its characteristics and implications. However, many aspects of the mechanisms underlying calcification remain unclear. A deeper understanding of the detailed nature and mechanisms of vascular calcification will not only improve the risk stratification, but also lead to the development of new therapies aimed at suppressing cardiovascular events and improving the patient outcomes. Continued research in this area is essential to advance our knowledge and treatment of coronary artery disease.

Author contributions

Teruo Sekimoto, Takamasa Tanaka, Tatsuya Shiraki and Renu Virmani: Conceptualization; Aloke V. Finn: Supervision; Teruo Sekimoto: Writing—original draft.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

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