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Is Preclinical Autoimmunity Benign?:

The Case of Cardiovascular Disease

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INTRODUCTION

Preclinical autoimmunity, or the presence of autoantibodies before disease symptoms, has been well described for several autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, and antiphospholipid antibody syndrome (APS).^{1–7} In studies of preclinical autoantibodies before SLE development, Arbuckle and colleagues² noted that autoantibodies less commonly associated with clinical sequelae of SLE such as antinuclear antibodies (ANA), anti-Ro, and antiphospholipid antibodies (APA) were present in the preclinical period more remote to clinical illness, whereas antibodies more specific for pathogenic features of SLE such as anti-Smith, antibodies against double-stranded DNA (dsDNA), and ribonucleoprotein (RNP) developed later, simultaneous to the onset of clinical features of SLE. Thus, benign autoimmunity was used to describe the earlier phase of autoantibody appearance during the preclinical period (Fig. 1). Certainly, there are many examples of autoantibodies occurring in disease-free individuals: RA-related autoantibodies and ANA occur in increased number and titer with age-related loss of tolerance^{8–11}; healthy relatives of individuals with autoimmune rheumatic diseases also have increased rates of autoantibody positivity.^{9,12,13} However, although ANA, rheumatoid factor, and APA may occur in the general population, individuals with such autoantibodies are also at increased risk for development of autoimmune rheumatic disease, with odds estimated as high as 10-fold to 30-fold.^{6,7}

Autoantibodies are markers for autoreactive B-cell activation, which can drive disease pathogenesis through a variety of mechanisms. Autoreactive B cells lead to the generation of autoantibody-secreting plasma cells, formation of immune complexes, presentation of

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autoantigens to T cells and costimulation, as well as the production of proinflammatory cytokines, chemokines, and lymphangiogenic growth factors. But when does benign become pathogenic autoimmunity during disease development? Early on, autoantigens activate self-reactive B cells, leading to the formation of short-lived plasma cells secreting autoantibodies. However, if self-reactive B cells enter germinal centers, they may undergo somatic hypermutation and affinity maturation of B-cell receptors, immunoglobulin class switching, generation of long-lived self-reactive B cells, and differentiation into long-lived plasma cells secreting high-affinity Fc receptor-binding autoantibodies.^{14,15} An example of such a transition is the formation of the ectopic tertiary lymphoid structures in the RA synovium, which clearly leads to the pathogenic autoimmune features of RA.^{16,17}

As described in detail elsewhere in this issue of *Rheumatic Disease Clinics*, the identification of preclinical autoimmunity before rheumatic disease development has led to substantial efforts to accurately describe autoimmune rheumatic disease pathogenesis such that individuals might be identified and targeted for primary prevention strategies, or secondary prevention strategies in the case of early disease features not yet meeting disease classification criteria. Recent data suggest that autoantibodies might be risk factors for development of cardiovascular disease (CVD) as well.

ANTIPHOSPHOLIPID ANTIBODIES, RHEUMATOID ARTHRITIS-RELATED AUTOANTIBODIES, AND CARDIOVASCULAR DISEASE, AS WELL AS SUBCLINICAL ATHEROSCLEROSIS, IN PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASE

Patients with RA have an increased risk for CVD of 1.5-fold to 2-fold, comparable with the risk in type II diabetes mellitus.^{18,19} Moreover, the presence of traditional risk factors does not fully account for this degree of excess risk. Therefore, it has been proposed that autoimmune-mediated inflammation may contribute to increased CVD risk in RA.²⁰ RA-related autoantibody positivity has been associated with increased risk of CVD events among patients with RA.^{21–23} There is an increased prevalence of subclinical measures of atherosclerosis in RA,²⁴ and antibodies to modified citrullinated vimentin and anticyclic citrullinated peptide antibodies (anti-CCP) have been correlated with carotid intima media thickness (IMT) in early RA.^{25,26}

CVD is a leading cause for mortality in SLE,²⁷ and given that APA are present in greater abundance in SLE compared with the general population, they have been evaluated as potential risk factors for CVD in SLE. In a large US prospective cohort of patients with SLE evaluated for myocardial infarction (MI) and subclinical atherosclerosis, patients with history of positivity for the lupus anticoagulant had a higher prevalence of history of MI (22% vs 9%, $P = .04$).²⁸ In a unique prospective study for hard clinical cardiovascular end points in 182 Swedish patients with SLE free from CVD at baseline, Gustafsson and colleagues²⁹ found that presence of any anticardiolipin autoantibodies (aCL) or anti- β 2 glycoprotein (anti- β 2GPI) autoantibodies were strongly associated with an increased risk of first CVD events over a mean of 8.3 years (hazard ratio [HR] 4.9, 95% confidence interval [CI] 1.76, 17.72). In contrast, anti-Smith, anti-dsDNA, and RNP had lower point estimates

for this association, but these did not reach statistical significance. In a follow-up of 208 patients with SLE in the same inclusion cohort over 12 years, presence of any APA was predictive of cardiovascular mortality (HR 2.8, 95% CI 1.1–1.7) and again, whereas specific antidsDNA antibodies were associated with noncardiovascular mortality, they were not associated with cardiovascular mortality.³⁰ Moreover, levels of aCL and anti- β 2GPI autoantibodies were also associated with myocardial perfusion defects detected by single-photon emission computed tomography, but not in the distribution of major coronary arteries, suggesting that APA may also cause small, undetected thrombi in the coronary microcirculation.³¹

Previously, there was no known association in patients with SLE between APA and coronary artery calcification (CAC), a marker of overall atherosclerotic burden.²⁸ However, in a small group of patients with SLE (N = 60), Plazak and colleagues³² recently reported an increased risk of CAC in patients with both increased aCL and anti- β 2GPI IgG levels, and among 139 patients with SLE, Romero-Diaz and colleagues³³ reported increased levels of aCL in those with CAC.

ANTIPHOSPHOLIPID ANTIBODIES, ANTINUCLEAR ANTIBODIES, AND RHEUMATOID ARTHRITIS-RELATED AUTOANTIBODIES AND CARDIOVASCULAR DISEASE, AS WELL AS SUBCLINICAL ATHEROSCLEROSIS, IN PATIENTS WITHOUT AUTOIMMUNE RHEUMATIC DISEASE

The increased prevalence of CVD in autoimmune rheumatic diseases such as RA and lupus, and the increased risk of CVD in patients with rheumatic disease with autoantibodies suggest that CVD may have autoimmune features. Studies identifying relationships between autoantibodies and cardiovascular outcomes in individuals without clinically active autoimmune diseases certainly support the role of autoimmunity in the pathogenesis of CVD. In 3 general population samples,^{34–36} RF positivity has been associated with ischemic heart disease. Tomasson and colleagues³⁶ reported an increased risk of cardiovascular mortality in RF-positive patients followed prospectively over 23 years in their Icelandic Reykjavik population-based cohort, even after excluding participants with any joint symptoms (HR 1.60, 95% CI 1.08–2.37). Also, in a recent nested case-control study within a cohort of middle-aged healthy UK men followed for CVD,³⁷ participants with anti-CCP2 positivity had more ischemic heart disease (odds ratio [OR] 4.23, 95% CI 1.22–14.61). We measured the association of RA-related autoantibodies with CAC, using data from a community-based sample of 6814 men and women enrolled in the MESA (Multi-Ethnic Study of Atherosclerosis) trial.³⁸ Although we found that RA-related autoantibodies were associated with CAC in African American and white women, these data need to be verified in other general population cohorts without clinically active RA, and associations between RA-related autoantibodies and IMT need to be investigated.

Although there is a paucity of studies identifying clear-cut associations between specific ANA and cardiovascular outcomes in patients with SLE, one study evaluating patients

without SLE presenting with chest pain³⁹ found that patients with triple vessel coronary artery disease had higher odds of positive ANA (OR 11.67, 95% CI 3.91–17.82) compared with controls with negative angiograms. In addition, in a population-based cohort study of 7852 patients who had ANA testing, Liang and colleagues³⁵ found that a positive ANA was associated with risk of MI, independent of the presence of SLE diagnosis (HR 1.29, 95% CI 1.03–1.61). Furthermore, there are numerous studies reporting associations between APA and cardiovascular outcomes in individuals without autoimmune rheumatic diseases. In particular, in several studies,^{40–49} APA have been found in the sera and plaques of individuals with clinical cardiovascular events. A few studies have reported positive correlations between APA and IMT, and in a case-control study of 50 male patients with acute MI, Dropinski and colleagues⁴² found APA level to be higher in MI cases, and APA level correlated with IMT as well.^{50,51} Although previous studies in individuals without SLE did not identify associations between APA and CAC,^{45,52} we did find associations when we tested the hypothesis that circulating APA are associated with subsequent subclinical atherosclerosis, measured as CAC in a cohort of community-based African American and white young adults followed prospectively for subclinical and clinical cardiovascular outcomes in the CARDIA (Coronary Artery Risk Development in Young Adults) study.⁵³ After adjustment for traditional cardiovascular risk factors, APA were associated with subclinical atherosclerosis measured as CAC greater than 0 after 15 years of follow-up. IgG and IgA anti- β 2GPI antibodies were associated with CAC greater than 0 measured after 15 years of follow-up (anti- β 2GPI IgG: OR 6.4, 95% CI 2.4–16.8; IgA: OR 5.6, 95% CI 2.3–13.2). Anti- β 2GPI IgM was marginally associated with CAC greater than 0 (IgM: OR 1.7, 95% CI 1.0–3.1), and aCL IgG were also associated with CAC greater than 0 (OR 5.1, 95% CI 1.4–18.6). Associations between rheumatic disease autoantibodies and subclinical and clinical atherosclerosis in individuals without rheumatic disease have led us to propose a possible model in which preclinical autoantibodies are not only risk factors for connective tissue disease development but also for subclinical and clinical CVD (Fig. 2), and their association with CVD development might occur in parallel with, or even independent of the presence of autoimmune rheumatic diseases.

POSSIBLE MECHANISMS FOR ASSOCIATIONS BETWEEN AUTOANTIBODIES AND ATHEROSCLEROSIS

As reported elsewhere in this issue, there is abundant evidence that autoimmune processes occur before clinical diagnosis of RA and SLE. Work by Maradit-Kremers and colleagues⁵⁴ furthermore reported that in the preclinical period of RA development, pre-RA cases already had increased risk for coronary heart disease. In their landmark retrospective longitudinal RA incidence cohort study within the Rochester Epidemiology Project, during the preclinical period 2 years before RA diagnosis, cases had increased odds of acute MI (OR 3.17, 95% CI 1.16–8.68), sudden death (HR 1.94, 95% CI 1.06–3.55), and unrecognized MI (OR 5.86, 95% CI 1.29–26.64) compared with controls. Therefore, autoimmune-mediated processes occurring during the preclinical period may lead to coronary artery disease development. Sokolove and colleagues⁵⁵ reported citrullinated proteins within atherosclerotic aorta segments from men without autoimmune rheumatic diseases. These citrullinated proteins were also recognized by anti-citrullinated peptide antibodies (ACPAs)

derived from patients with RA, indicating that ACPAs might propagate the progression of atherosclerosis. In addition, the previous findings of associations between APA and subclinical atherosclerosis suggest that the role of APA in the pathogenesis of atherosclerosis is not merely prothrombotic. This theory has been explored in animal models. Both monoclonal aCL bound to β 2GPI and anti- β 2GPI IgG derived from an APS mouse model enhanced oxidized low-density lipoprotein (LDL)/ β 2GPI complex binding to macrophages, and oxidized LDL uptake by macrophages promotes foam cell formation.^{56,57} Moreover, APA increased atherosclerotic lesions in a mouse model of atherosclerosis, the LDL-receptor knockout mouse (LDL-RKO): mouse aCL, induced by immunization of LDL-RKO mice with human aCL, led to increased fatty streak formation,⁵⁸ and immunization of LDL-RKO mice with β 2GPI also led to accelerated atherosclerotic lesions.⁵⁹ These mechanistic studies lend biological plausibility to the theory that autoantibodies are direct risk factors for atherosclerosis.

FUTURE CONSIDERATIONS

These collective data indicate that preclinical autoimmunity or autoimmunity in individuals without clinically apparent disease are decidedly not benign. Numerous studies indicate autoantibodies might be markers for humoral and cell-mediated immune mechanisms driving CVD not only in individuals with but also in those without autoimmune rheumatic diseases. For patients with active RA, the European League Against Rheumatism⁶⁰ recently recommended annual cardiovascular risk assessment and management. Moreover, evidence is increasing for risk reduction from pharmaceutical interventions in active RA, such as anti-tumor necrosis factor α , hydroxychloroquine, statins, and possibly, methotrexate.^{19,20} Because it has recently been shown that both rheumatologists and primary care physicians identify and manage cardiovascular risk factors less often in patients with RA compared with controls from the general population, interventions may be needed to improve CVD risk in patients with RA.^{19,60–62} Potential preventive interventions for CVD development in SLE are of course being proposed as well.⁶³ It seems that the presence of autoantibodies might also be a pertinent risk marker for subclinical atherosclerosis and clinical CVD in the general population as well. Although further studies are needed to confirm the relevance of autoantibodies as CVD risk markers, we propose that preclinical autoimmunity might one day enable clinicians to identify individuals in the general population who might benefit from traditional risk factor assessment and measures targeted at CVD prevention, perhaps even measures targeting the process of autoimmunity.

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KEY POINTS

- Preclinical rheumatic disease–related autoantibodies have been identified in stored samples before development of systemic lupus erythematosus and rheumatoid arthritis (RA).
- Autoreactive B cells can drive RA pathogenesis through generation of autoantibody-secreting plasma cells, presentation of autoantigens such as citrullinated peptides to T cells, production of proinflammatory cytokines, and formation of ectopic tertiary lymphoid structures, as are found in the RA synovium.
- It has been hypothesized that atherosclerosis might have autoimmune features because of the involvement of autoantigens and their autoantibodies in atherogenesis in both humans and animal models.
- Antiphospholipid antibodies, antinuclear antibodies, and RA–related autoantibodies have been associated with atherosclerosis in clinically active rheumatic diseases as well as in general population study samples.

Fig. 1.

Phases in the development of pathogenic autoimmunity. Normal immunity progresses to benign autoimmunity through the influence of genetic composition and environment. Later, benign autoimmunity progresses to pathogenic autoimmunity. Symptoms of clinical illness appear soon after pathogenic autoimmunity develops. (From Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1532; with permission.)

Conceptual Model for the Relationship between Autoimmunity and Cardiovascular Disease Development

Fig. 2.

Connective tissue disease (CTD)-related autoimmunity might lead to inflammation and epitope spreading, which can progress to clinically active autoimmune CTD. It is hypothesized that the increased prevalence of atherosclerosis and subsequent cardiovascular events in autoimmune CTD is mediated by inflammation from disease activity. CTD-related autoimmunity might be independently associated with the development of atherosclerosis, which can be measured by the surrogate CAC or IMT. Subclinical atherosclerosis might then progress to clinical cardiovascular events.