

# Autoimmune Diseases Promoting Coronary Artery Disease in Women

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## BACKGROUND

Autoimmune diseases are systemic inflammatory conditions affecting different organs, including the cardiovascular system. These diseases are more common in women and are associated with premature atherosclerosis with development of coronary artery disease at an early age. In these cases, coronary artery disease may be the first manifestation or may appear when autoimmune disease has already been established. Multiple factors are responsible for this accelerated process.

According to the last guidelines for the prevention of cardiovascular disease in women, women with autoimmune conditions are considered to be "at risk". (1, 2) This means that women with this conditions are more likely to develop cardiovascular disease (CVD).

In this setting, the prevalence of ischemic heart disease has increased as a consequence of higher life expectancy in these patients due to improved therapy. (3) In turn, specific therapy for autoimmune diseases increases the risk of cardiovascular disease.

Premature coronary artery disease is the leading cause of morbidity and mortality in patients with connective tissue disorders. (4, 5)

The goal of this review is to update the impact of autoimmune diseases in coronary artery disease in women.

## SYSTEMIC LUPUS ERYTHEMATOSUS AND CARDIOVASCULAR DISEASE

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting the connective tissue and characterized by chronic inflammation and damage of body tissues mediated by the immune system, specifically due to binding of antibodies to body cells and to deposition of antigen-antibody complexes. This condition occurs 9 times more often in women than in men.

In women with SLE the risk of cardiovascular events is 5 to 6 times greater higher (6) and 50 times greater in the 35- to 44-year age group. (4) Although SLE may produce coronary arteritis, atherosclerosis is the most common cause of coronary artery disease.

The following factors are associated with the development of atherosclerosis:

1. Traditional coronary risk factors.
2. Chronic systemic inflammatory state.
3. Corticosteroids therapy and doses.

Traditional coronary risk factors are associated with the development of CVD. Hypercholesterolemia, hypertension and diabetes are more prevalent in SLE patients. (7) An abnormal lipid profile is seen in SLE, with a pattern characterized by low levels of LDL- and HDL-cholesterol and high levels of VLDL-cholesterol and triglycerides. (8)

Although SLE patients have greater prevalence of coronary risk factors, these factors alone do not completely explain the development of coronary artery disease. Certain other metabolic changes also occur more frequently in SLE, namely premature menopause, renal impairment, high triglycerides and high plasma homocysteine. (5) All these abnormalities also contribute to the development of CVD.

The other factors involved are chronic systemic inflammation with increased levels of cytokines, mediators of inflammation and adhesion molecules with endothelial dysfunction. (9)

This chronic process also modifies the lipid profile which also predisposes to coronary artery disease.

Corticosteroid therapy and dose are also involved in the development of coronary artery disease. As it has been reported several decades ago, treatment with these drugs for more than a year increases the prevalence of atherosclerosis. (10)

Corticosteroids, as prednisone, produce metabolic abnormalities, central obesity, hypertension, impaired glucose tolerance and abnormal lipid profiles, thus increasing the risk of cardiovascular events.

Of importance, these effects are not observed with low dose of corticosteroids (< 10 mg/day). Over the last years, the definition of "high doses" of prednisone was revised and changed to a cutoff value of > 6 mg/day, as the risk of events with lower doses is similar to the one observed in patients not taking corticosteroids. (11)

Antimalarial drugs as hydroxychloroquine have a beneficial effect, especially on lipids, and thus are not associated with the development of coronary artery

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disease.

Of importance, SLE is associated with the antiphospholipid syndrome, characterized by the production of autoantibodies involved in the development of cardiovascular disease (see antiphospholipid syndrome below).

Subclinical CVD can be evaluated by the presence of coronary calcifications in the computed tomography scan (coronary artery calcium score) Using this method, several studies have demonstrated an elevated prevalence in women with SLE. (12, 13) Subclinical CVD can also be evaluated by the presence and size of carotid artery plaque. The prevalence of carotid artery plaque is significantly higher in SLE women in the age group between 45-55 years compared with women without SLE (Figure 1). (14)

### RHEUMATOID ARTHRITIS AND CARDIOVASCULAR DISEASE

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is 2 to 4 times more common in women and is more frequent than SLE, particularly between 30-50 years of age.

Life expectancy is reduced due to premature atherosclerosis. The risk of cardiovascular events is 2 to 4 times greater according to different studies. (15, 16)

Similar to SLE, the presence of traditional coronary risk factors is important for the development of CVD. Smoking is the most prevalent risk factor. Moreover, cigarette smoking has proved to increase the risk of RA. (17)

Systemic inflammation plays a key role in the

pathogenesis of CVD through mediators of inflammation. C-reactive protein predicts cardiovascular mortality in these patients. (18)

Treatment of inflammation reduces the risk of cardiovascular events. As in the case of SLE, corticosteroids should be avoided to prevent the development of atherosclerosis.

The use of methotrexate for the control of inflammation has proved to reduce cardiovascular mortality. (19)

Treatment of RA with biological agents (anti-tumor necrosis  $\alpha$  therapy) as adalimumab, etanercept, infliximab, abatacept, anakinra and rituximab, reduces mortality, particularly in patients with favorable response to treatment. (20)

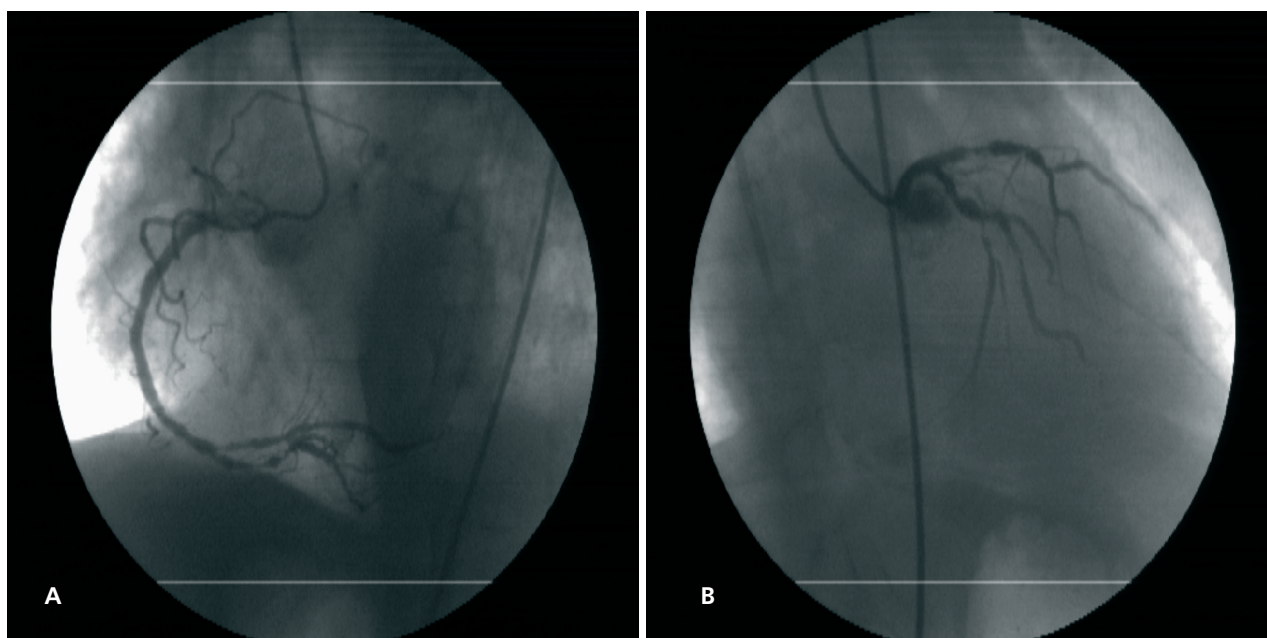
### VASCULITIS AND CARDIOVASCULAR DISEASE

Primary systemic vasculitis includes a group of autoimmune disorders characterized by necrotizing inflammation of blood vessels.

Systemic inflammation and ischemia produce vessel occlusion and stenosis of the vessels. The following disorders are included: giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, Kawasaki disease and Henoch-Schönlein purpura.

Several factors should be considered for the development of atherosclerosis, particularly:

1. Excessive inflammation and remodeling of blood vessels.
2. Accumulation and of oxidized LDL
3. Long-term therapy with high-dose of corticosteroids. (21)



**Fig. 1.** Images of a 42-year old woman with SLE, undergoing dialysis for chronic renal failure, she is admitted by with acute coronary syndrome. Coronary angiography shows extensive coronary lesion. Unsuccessful anterior descending artery angioplasty was performed. **A.** Right coronary artery with wire in left axial oblique view. **B.** Left coronary artery in left anterior oblique view.

### Takayasu's disease

Takayasu's disease is an idiopathic granulomatous vasculitis of the great vessels, affecting the aorta and its main branches. It is a rare condition, more common in Japan. Women are 6 to 10 times more likely to be affected than men.

The patients may develop arterial stenosis or aneurysms, yet stenosis is three to four times more frequent. The clinical presentation includes intermittent claudication of the extremities, murmurs, and asymmetrical pulses and blood pressure levels. Hypertension occurs in 40% to 90% of cases and is related with stenosis of the renal artery. Blood pressure differences between the arms and the aorta are common due to stenosis of the subclavian artery and of the innominate artery. (22)

Vasculitis of the coronary arteries is uncommon and affects mostly the coronary ostium and the proximal segments.

The complications are related with to aortic aneurysm and uncontrolled hypertension.

These patients respond to corticosteroid therapy and recurrences can be treated with cyclophosphamide or methotrexate.

Surgery is indicated for symptomatic stenosis of the subclavian arteries or carotid arteries using grafts in the aortic root (as stenosis of the ascending aorta stenosis is rare) (Figure 2).

### Antiphospholipid syndrome

The antiphospholipid syndrome (APS), first described in 1983, was defined as a triad including venous or arterial thrombosis, pregnancy morbidity (miscarriages, recurrent fetal death and prematurity) and hematological disorders (thrombocytopenia and hemolytic anemia), associated by due to elevated antiphospholipid antibodies (aPL), lupus anticoagulant and/or anticardiolipin antibodies.

APS is an autoimmune disease characterized by the clinical association of antiphospholipid antibodies with hypercoagulable state and high risk of venous and arterial thrombosis. (24, 25)

The disease is classified as primary (PAPS) when it occurs in the absence of any features of other autoimmune disease, and secondary where another autoimmune disease is present (SAPS).

Venous thromboses are more common than arterial thromboses, and deep venous thrombosis (DVT) of the inferior extremities is the most frequent location. Arterial thrombosis is most frequent in the cerebral arteries. Some authors have found a relation between the site of thrombosis and the type of aPL antibodies. DVT and pulmonary thromboembolism are more common in patients with lupus anticoagulant, while involvement of the coronary arteries, cerebral arteries and peripheral arteries is more frequently associated with elevated IgG or IgM anticardiolipin antibodies. (26)

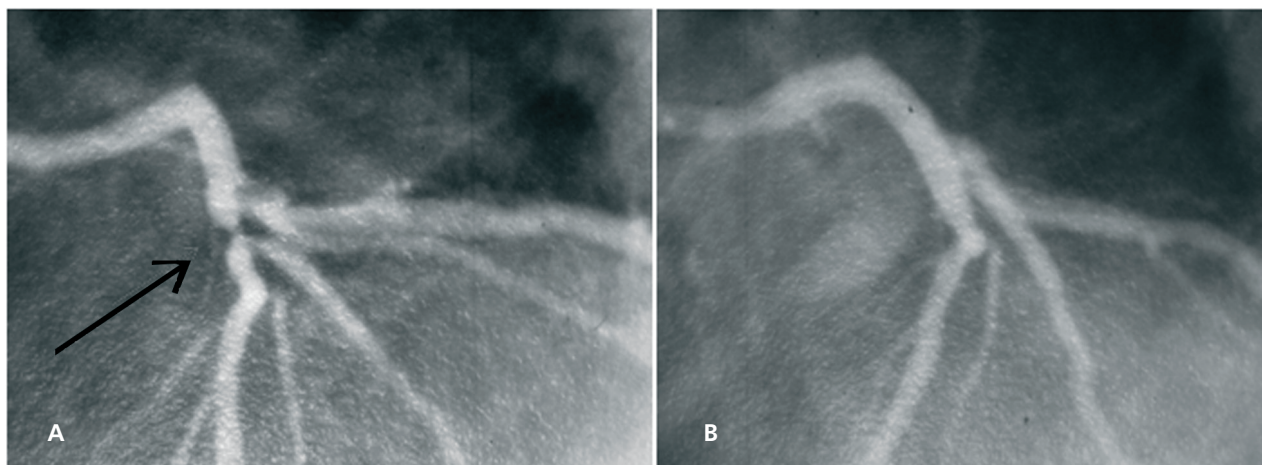
Antiphospholipid syndrome is associated with myocardial infarction, intracardiac thrombi and pulmonary hypertension which predisposes to thrombosis and, less frequently, with valvular heart disease and atherosclerosis of peripheral and coronary arteries. This might be explained by the pro-inflammatory and procoagulant effects of antibodies acting directly in endothelial cells. (25)

As we have already mentioned, SLE is also characterized by the production of autoantibodies as lupus anticoagulant and anticardiolipin antibodies which are associated with high risk of thrombosis. These antibodies are commonly found in SLE patients who are more likely to develop antiphospholipid syndrome.

Traditionally, acute myocardial infarction in the setting of APS is more common in women, in patients < 45 years, accompanied by with another thrombotic event, in whom smoking exerts an additive effect (Figure 3). (27)



**Fig. 2.** Images corresponding to a 22-year old woman with Takayasu's disease, hypertension, carotid obstruction and aortic regurgitation. After confirming renal artery lesion, she undergoes successful angioplasty. Renal artery lesion (A) with angioplasty balloon inflation (B) and successful outcome (C).



**Fig. 3.** Images of a 38-year old woman, current smoker and under oral contraceptive treatment. She is hospitalized due to angina following a 3-week evolution anterior myocardial infarction . A successful angioplasty was performed. The patient progresses with femoral vein thrombosis at the puncture site. Antiphospholipid syndrome is suspected and antiphospholipid antibodies are positive for anticardiolipine. Anterior descending artery before (A) and after (B) angioplasty.

**CONCLUSIONS**

Over the last years, we have become aware of the fact that cardiovascular disease is not limited to men and affects women in an aggressive way.

Autoimmune diseases constitute a special chapter of cardiovascular disease in women, as they generate premature atherosclerosis which is the leading cause of mortality in these patients.

In this kind of patients, physicians should be alert to the cardiovascular risk association with this conditions. It’s importance to early detection and to indicate the adequate treatment for cardiovascular disease.

**Conflicts of interest**

None declared.

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