Review Article

Estrogen in Cardiovascular Disease during Systemic Lupus Erythematosus

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ABSTRACT

Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that disproportionately affects women during their childbearing years. Cardiovascular disease is the leading cause of mortality in this patient population at an age when women often have low cardiovascular risk. Hypertension is a major cardiovascular disease risk factor, and its prevalence is markedly increased in women with SLE. Estrogen has traditionally been implicated in SLE disease progression because of the prevalence of the disease in women; however, its role in cardiovascular risk factors such as hypertension is unclear. The objective of this review is to discuss evidence for the role of estrogen in both human and murine SLE with emphasis on the effect of estrogen on cardiovascular risk factors, including hypertension.

Methods: PubMed was used to search for articles with terms related to estradiol and SLE. The references of retrieved publications were also reviewed.

Findings: The potential permissive role of estrogen in SLE development is supported by studies from experimental animal models of lupus in which early removal of estrogen or its effects leads to attenuation of SLE disease parameters, including autoantibody production and renal injury. However, data about the role of estrogens in human SLE are much less clear, with most studies not reaching firm conclusions about positive or negative outcomes after hormonal manipulations involving estrogen during SLE (ie, oral contraceptives, hormone therapy). Significant gaps in knowledge remain about the effect of estrogen on cardiovascular risk factors during SLE. Studies in women with SLE were not designed to determine the effect of estrogen or hormone therapy on blood pressure even though hypertension is highly prevalent, and risk of premature ovarian failure could necessitate use of hormone therapy in women with SLE. Recent evidence from an experimental animal model of lupus found that estrogen may protect against cardiovascular risk factors in adulthood. In addition, increasing evidence suggests that estrogen may have distinct temporal effects on cardiovascular risk factors during SLE.

Implications: Data from experimental models of lupus suggest that estrogens may have an important permissive role for developing SLE early in life. However, their role in adulthood remains unclear, particularly for the effect on cardiovascular disease and its risk factors. Additional work is needed to understand the effect of estrogens in human SLE, and preclinical studies in experimental models of SLE may contribute important mechanistic insight to further advance the field. (*Clin Ther*. 2014;36:1901–1912)

Key words: estrogen, hypertension, immune, inflammation, lupus.

BACKGROUND

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown cause with multiple genes, environmental factors, and sex hormones likely playing roles in its pathogenesis.[1] SLE is characterized by a loss of tolerance to self-antigens

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which leads to the production of autoantibodies to the nucleus, most commonly anti–double-stranded DNA (anti-dsDNA) antibodies.[2] These autoantibodies contribute to immune complex formation and can deposit within virtually every tissue in the body, leading to inflammation and tissue injury, thus producing the clinical symptoms experienced by patients.[2] Malar rash, discoid rash, photosensitivity, pleuritis, pericarditis, nonerosive arthritis, neurologic disorders such as seizures and psychosis, and hematologic disorders such as hemolytic anemia and thrombocytopenia are all clinical symptoms of SLE[3] (Table I). The kidneys are commonly affected in patients with SLE with a high prevalence of immune complex-mediated glomerulonephritis, and the leading cause of mortality in these patients is cardiovascular disease.[4,5] Although its cause is multifactorial, it is clear that SLE has a strong predilection for females, especially during their childbearing years.[6] When disease onset occurs between menarche and menopause, the female-to-male ratio is 9:1.[7] However, SLE diagnosis before the onset of puberty and after menopause, although still favoring women, lacks a strong a female-to-male ratio.[8] This predilection for women during their reproductive years suggests the possibility of a role for sex steroids, especially estrogen, in the pathology of SLE and contributes to the controversy surrounding manipulation of estrogen through oral contraceptives and hormone therapy (HT) in women with SLE. Although estrogens are widely perceived as contributing to SLE disease progression, the effect of estrogens on cardiovascular risk factors during SLE remains unclear.

METHODS

Articles were identified through a PubMed search that used key words related to estrogen and SLE. References from retrieved publications were also examined.

FINDINGS

Cardiovascular Disease in SLE

SLE disease is associated with a bimodal pattern of mortality.[5] Death early in the disease often results from increased rate of infection in patients with active disease in part because of immunosuppression from conventional treatments for SLE. In contrast, death later in the course of SLE most often occurs during inactive disease and is primarily a result of cardiovascular problems and atherosclerotic heart disease. Despite the improvement in the prognosis of SLE, cardiovascular disease has emerged as a major problem for patients with SLE at increased risk for stroke, atherosclerosis, and myocardial infarction.[9–11] In one cohort of 9547 patients, patients with SLE had not only an increased risk of death in comparison with the general population but also an increased risk of death due to circulatory or cardiovascular disease.[4] Studies in other cohorts of SLE also support a link

Table I. Diagnostic criteria for SLE.

Criterion	Description
Malar rash	Erythema over the malar eminence (characteristic butterfly rash)
Discoid rash	Erythematosus patches
Photosensitivity	Skin rash on exposure to sunlight
Oral ulcers	Oral or nasopharyngeal ulceration
Serositis	Pleuritis, pericarditis, pleural effusion, friction rub
Renal disorder	Proteinuria >0.5 g/d, immune complex–mediated glomerulonephritis
Neurologic disorder	Psychosis, seizures
Hematologic disorder	Hemolytic anemia, leukopenia, thrombocytopenia
Immunologic disorder	Anti-dsDNA antibody, anti-Sm antibody, lupus anticoagulant
Positive ANA	Abnormal titer of ANA

Four of 11 diagnostic criteria are required for diagnosis of SLE.
ANA = antinuclear antibody; Anti-dsDNA = anti–double-stranded DNA; anti-Sm = anti Smith; SLE = systemic lupus erythematosus.