Canadian Journal of Cardiology 34 (2018) 381–389

Review

Atherosclerotic Heart Disease in Women With Autoimmune Rheumatologic Inflammatory Conditions

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ABSTRACT

Women have a higher prevalence of several inflammatory rheumatologic conditions. These include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) to name a few. These conditions are all associated with higher rates of cardiovascular (CV) morbidity and mortality, which is driven primarily by atherosclerotic heart disease. Traditional risk factors are important considerations in the assessment of CV risk in the rheumatologic patient; however, these factors do not appear to impart a similar weight of risk in women with inflammatory autoimmune rheumatologic conditions. In addition, even when controlling for traditional risk factors, patients with RA or SLE continue to have a higher risk of CV events, which has been linked to the burden of systemic inflammation. Currently, the CV risk scoring systems available for the general population underestimate the burden of the problem in these complex patients. The increased CV risk in patients with rheumatologic diseases has been

RÉSUMÉ

Plusieurs affections rhumatismales inflammatoires ont une prévalence plus élevée chez les femmes, notamment le lupus érythémateux disséminé (LED), la polyarthrite rhumatoïde (PR) et la sclérodermie généralisée (SG). Ces affections sont toutes associées à des taux plus élevés de morbidité et de mortalité cardiovasculaires (CV), essentiellement attribuables à l'athérosclérose. Il importe de considérer les facteurs de risque classiques dans l'évaluation du risque CV chez les patients atteints d'affections rhumatismales; cependant, ces facteurs ne semblent pas se traduire par un risque similaire chez les femmes atteintes d'affections rhumatismales inflammatoires autoimmunes. En outre, même quand on tient compte de facteurs de risque classiques, les patients atteints de PR ou de LED demeurent plus à risque d'événements cardiovasculaires, ce qui a été mis en relation avec les répercussions de l'inflammation généralisée. Actuellement, les systèmes d'évaluation du risque CV au sein de la population

Cardiovascular disease (CVD) is the leading cause of death in women in developed countries.[1] Coronary artery disease (CAD) is the primary vehicle by which increased CVD risk occurs. In the general population, CAD manifests later in women and is frequently associated with an atypical presentation that complicates early diagnosis and treatment when compared with men. Both short- and long-term survival after acute myocardial infarction (MI) has been reported to be lower in women than in men.[2,3]

Chronic inflammatory rheumatologic conditions (chronic inflammatory disease [CID]), which may potentiate CV risk, are considerably more prevalent in women than in men. Women compose up to 90% of patients with SLE or SSc and 75% of patients with RA.[4] The combination of the incremental risk resulting from CID and the underdiagnosis of CV conditions in general render women with CID prone to complications from atherosclerotic vascular disease.

Chronic inflammatory autoimmune diseases have various cardiovascular (CV) manifestations such as pericarditis, vasculitis, aneurysms, and myocarditis. However, atherosclerosis, leading to ischemic heart disease (IHD) and cerebrovascular disease, carries the greatest CV risk for these patients. The reasons underlying the increased prevalence of CVD observed in this population is multifactorial. Although traditional CV risk factors certainly play an important role, their effects may differ in the patient with a rheumatologic condition. However, even after optimal control of traditional risk factors, a significant residual risk remains, which is related to the presence of chronic inflammation.

This review is intended to focus primarily on the relationship between chronic inflammatory rheumatologic conditions and atherosclerotic cardiovascular disease (ASCVD) in women.

Epidemiology of Atherosclerosis in Chronic Inflammatory Conditions

In autoimmune diseases, the immune response to self-antigens results in the damage or dysfunction of tissues, which affects specific organs or body systems but is also

Received for publication December 19, 2017. Accepted January 16, 2018.

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See page 386 for disclosure information.

https://doi.org/10.1016/j.cjca.2018.01.015

reported in the literature for years but remains underrecognized by internists and cardiologists. Although these conditions themselves are relatively rare, the further study of inflammation and its treatment in CV disease will be beneficial to the general population.

générale sous-estiment les répercussions de la problématique dans ces cas complexes. L'accroissement du risque CV chez les patients atteints d'affections rhumatismales est signalé dans la littérature depuis des années, mais il demeure insuffisamment reconnu par les internistes et les cardiologues. Bien que ces affections soient relativement rares, l'étude plus poussée de l'inflammation et de son traitement dans les cas de maladie CV sera salutaire pour l'ensemble de la population.

observed systemically. For most systemic autoimmune disorders, there is a clear difference in prevalence by sex, making this a more common CV risk factor in women.

The association between CID and increased CV mortality has been reported in the literature for decades. The driver of this higher risk is related to atherosclerotic CVD.[5] Although systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have the largest body of available literature describing the increased burden of ASCVD, smaller studies suggest that other inflammatory conditions have similarly increased atherosclerotic risk. CIDs are estimated to afflict up to 7% of the general population.[4] RA is by far the most common autoimmune disease and is characterized by systemic inflammation of the joints resulting from autoantibodies (particularly rheumatoid factor and citrullinated peptide), causing in joint swelling and pain. The course of disease can vary from severe joint inflammation and early joint destruction to milder manifestations but typically includes symmetrical polyarthritis of the hands and feet. RA occurs in approximately 1% of white women in the United States.[6] The incidence rate for RA is 40 per 100,000 population and affects women up to 3 times more often than men. The mean age at onset is 56 years. Higher rates of death were noted in the patient with RA, with women having more excessive mortality compared with men.[7] The increased morbidity and mortality in RA has been found to result from ASCVD, resulting in an up to 3-fold higher risk of CV mortality from events such as MI or stroke.[8] In fact, women with RA have a higher risk of MI than do men with RA.[9] Besides a higher risk of CVD developing, patients with CID have adverse outcomes after CV events, including more complications after CV interventions, such as in-hospital mortality or ischemic events after first-time coronary intervention or stroke.[10,11]

SLE is a rare autoimmune disease that causes tissue damage by autoantibodies and immune complexes. SLE has a wide range of clinical manifestations and can affect the joints and many organs, such as kidney, skin, lung, nervous system, or heart. SLE affects about 5 to 6 individuals per 100,000 population, 90% of whom are women. Ethnicity plays a major role in SLE prevalence. African American, Hispanic, Asian, and Native American women are 2 to 3 times more likely to experience SLE compared with white women.[12] SLE can have an onset at any point in life but typically is seen most commonly between the ages of 16 and 55 years. The higher female proportion of patients with SLE has been partially accredited to a hormonal effect that may explain the different male-to-female ratios of SLE observed according to age. In children, in whom the effect of sex hormones is minimal, the male-to-female ratio is 1:3, increasing in adult women of childbearing age to a ratio up to 1:15. In older postmenopausal women, this ratio lowers slightly to a male-to-female ratio of 1:8.[13] Patients with SLE have markedly higher morbidity and mortality associated with CVD.[11] Women between 35 and 45 years of age have a particularly high risk, with the relative risk of MI increased to more than 50 times compared with age-matched controls in the general population.[14-16] This relative risk flattens out in older women but is still 2- to 5-fold higher in women older than 55 years.[17] Classically, SLE has been shown to have a bimodal mortality rate.[18] Early, typically within 3 years of diagnosis, patients with SLE present with disease activity—related complications such as sepsis or kidney disease. With current aggressive treatment approaches, this early mortality from acute SLE has decreased significantly. Consequently, the incidence of CV mortality that occurs later in the course of the disease is increasing. Notwithstanding, renal failure caused by SLE may have an additive role in the development of atherosclerosis.[19] It is important to mention that SLE in men seems to differ clinically, because men have worse SLE-related outcomes compared with women. Data from experimental models of SLE suggest that estrogens may have an important permissive role for the development of SLE early in life. However, their role in adulthood remains unclear, particularly their effect on CVD and its risk factors.[20]

Systemic sclerosis (SSc) is a rheumatic autoimmune disease characterized by small-vessel vasculopathy, occurrence of autoantibodies, and fibrosis of both the skin and internal organs, resulting in thickening of the skin, pulmonary arterial hypertension, interstitial lung disease, and gastrointestinal manifestations. SSc affects approximately 28 individuals per 100,000 adults in the United States alone and has a 5-fold higher female prevalence compared with men.[21] The annual incidence rate is described as being as high as 1.9 per 100,000 population per year.[21] SSc has a higher prevalence at a younger age in African Americans than in white individuals.[22] SSc affects the microcirculation and injures the endothelium, presenting as Raynaud's phenomenon, pulmonary arterial hypertension, and renal crisis.[23,24] Endothelial dysfunction and inflammation can lead to macrovascular dysfunction and ultimately atherosclerosis. Estimating cardiac involvement in SSc is challenging because it can manifest in various ways, such as myocardial damage, fibrosis of the conduction system, or pericardial or valvular disease.[25] The risk of MI is increased approximately 2-fold when compared with controls. The association of SSc with atherosclerosis is not fully understood but seems to result from underlying systemic inflammation, endothelial wall damage, and vasculopathy.[26] Fewer than 40% of patients with SSc and CVD have obstructive CAD, indicating that microvascular abnormalities may be the primary mechanism leading to CV events.[27] Compared with RA and SLE, fewer studies address atherosclerotic changes in SSc.