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Non-traditional risk factors for atherosclerotic disease: A review for emergency physicians

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ABSTRACT

Introduction: Acute coronary syndrome (ACS) is a life-threatening disease frequently managed in the Emergency Department (ED). Risk factors such as age, hypertension, diabetes mellitus, obesity, and smoking are classically associated with atherosclerosis and ACS.

Objective: This review evaluates non-traditional risk factors for atherosclerotic disease and seeks to inform physicians of their potential danger, particularly in vulnerable patient populations.

Discussion: Traditional risk factors are commonly utilized in the evaluation of patients with concern for ACS and acute myocardial infarction (AMI), though these may not be as useful for individual patient assessment. Heart disease accounts for a significant number of deaths in the U.S. Awareness of disease presentation and risk factors is important; however, several non-traditional risk factors are associated with atherosclerosis. Vasculitides, as well as immunologic medications used to treat these patients, increase atherosclerosis. Specific types of cancer and some therapies used to treat cancer are associated with atherosclerosis development and cardiovascular disease (CVD). Heavy alcohol use increases atherosclerosis and risk of AMI. Pregnancy also increases risk of AMI. Patients with HIV develop atherosclerosis at higher rates, and antiretroviral therapy predisposes patients to early development of coronary disease. Infections such as pneumonia and sepsis, associated with elevated inflammation, increase rate of ACS events during illness and throughout the one-year period after diagnosis of infection.

Conclusions: Several non-traditional factors are associated with increased risk of atherosclerosis and ACS. Knowledge of these risk factors is important in the ED to minimize the potential of missing ACS.

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1. Introduction

Emergency physicians frequently manage patients with acute coronary syndrome (ACS) from atherosclerosis. The medical community has come to universally recognize the so-called “classic” risk factors for development of atherosclerosis, including age, hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking history, and family history (first degree relatives). Atherosclerosis is associated with ACS. Acknowledgment of these traditional risk factors is important, but there are many other diseases and exposures that should also be recognized when evaluating a patient in the emergency department (ED). Close to 12% of patients with acute myocardial infarction (AMI) will not demonstrate classic risk factors [1]. In 2013, total deaths associated with underlying cardiovascular disease (CVD) in the United States was approximately 1 out of every 7, which is decreased from approximately 1 out of every 3 [2,3]. The decrease in deaths from CVD is believed to be a result of evidence-based approaches towards secondary prevention in combination with public awareness of traditional cardiovascular disease risk factors with changes in lifestyle. Still, a total of 660,000 Americans are expected to have their first AMI or CVD-related death this year with atherosclerosis, 305,000 will have a recurrent event, and an additional 160,000 silent AMIs will also occur in the U.S. [2].

Emergency physicians are responsible for recognizing and treating initial presentations of patients with ACS, and physicians must not only be aware of atypical presentations of ACS, but also non-traditional risk factors for atherosclerosis and CVD.

2. Discussion

In addition to the regularly recognized risk factors attributable to atherosclerosis and CVD, there are several risk factors which are not described as often, especially for premature atherosclerosis, and therefore may be not be recognized. Additional risk factors for premature atherosclerosis include chronic kidney disease (CKD); vasculitides such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA); human immunodeficiency virus (HIV); history including malignancy, heavy alcohol use, or pregnancy; and the presence or recent history of severe systemic infection. This review will evaluate the evidence behind these risk factors.

2.1. Chronic kidney disease (CKD)

While there is controversy whether CKD is an independent cause of premature atherosclerosis, there is a clear relationship between patients who have CKD and incidence of ACS events. Individuals who have CKD are more likely to die from atherosclerosis and ACS events rather than progress to end-stage renal disease (ESRD). Mortality from CVD is 5 to 30 times higher in patients with end-stage renal disease (ESRD) when compared to patients of similar age, race, and sex [2].

There are multiple risk factors for CKD including autoimmune disease, systemic infection, drug exposure, urinary tract infections, urinary stones, urinary tract obstruction, and neoplasm; however, even when adjusting for these risk factors, there is an excessive risk for development of atherosclerosis and CVD [4]. Furthermore, CKD has a higher associated risk with recurrent CVD events than patients with diabetes, cigarette smoking, and metabolic syndrome [5].

Associated with renal disease, albuminuria or proteinuria has been shown in multiple studies to be an independent risk factor for cardiovascular events, congestive heart failure hospitalizations, and peripheral artery disease (PAD) [2].

2.2. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)

When examining what would normally be a younger and healthier population with no other risk factors, autoimmune disorders are a predisposing factor to the development of multiple health sequelae

including atherosclerosis and CVD. People with SLE are at risk for pericarditis, myocarditis, cardiac conduction abnormalities, and valvular disease, as well as atherosclerotic CVD. A systemic review of 28 studies examining the epidemiology of CVD in patients with SLE found that patients with SLE have at least double the risk of CVD with atherosclerosis as compared to the general population [6]. One study found that women aged 35–44 with SLE had 52.4 times an increased relative risk of AMI over 6.7 years as compared to a control group of women the same age group [7]. Another study conducted over 7 years in Sweden confirmed the previous findings that patients with SLE have a 2-fold increased risk of AMI as compared to the general population, but also found that pre-menopausal women with SLE aged 40–49 were found to have an 8.7-fold increased risk of AMI during that 7 year period [8]. The traditional cardiovascular risk factors, including hyperlipidemia, smoking, hypertension, and age are associated with 2- to 3-fold increases in atherosclerosis and CVD events, including death [6]. While the majority of patients with SLE are female, male patients with SLE have been shown to have a 4-fold increased risk of CVD events associated with atherosclerosis, as compared to females with SLE [9,10].

Similar to SLE, a meta-analysis of 24 studies concluded that patients with RA have a 59% higher risk of CVD mortality from atherosclerosis [11]. A positive antiphospholipid antibody titer has been identified as being associated with CVD related-mortality [6]. It is believed that the chronic inflammation may accelerate the progression of atherosclerosis in these diseases, yet the mechanism is not yet completely described.

Additionally, patients with autoimmune diseases and severe symptoms are more likely to be placed on corticosteroids and other immunosuppressive medications. Corticosteroids can exacerbate hyperlipidemia, hypertension, diabetes, and obesity, as well as atherosclerosis, increasing the risk of CVD in patients with autoimmune disorders [6,12]. Several studies have also shown that azathioprine use is an independent risk factor for development of peripheral arterial disease (PAD) and CVD events [13–15].

2.3. History of cancer

The type of cancer an individual has been diagnosed with, as well as current or prior treatments, affect the risk of developing atherosclerosis, CVD, and cardiac-related diagnoses. Survivors of Hodgkin lymphoma have been shown to have a higher risk of death from AMI with premature atherosclerosis. This may be related to supradiaphragmatic radiation therapy, as well as treatment with anthracycline or vincristine [16]. Several studies have estimated the increased risk of fatal CVD events in Hodgkin lymphoma survivors to range from 2.2 to 7.6-fold greater than the general population [16–18].

Cancer patients undergoing treatment with chemotherapy are at higher risk for cardiovascular complications, especially if they have a history of heart disease before treatment initiation. Patients with HER2 positive breast cancer undergoing treatment with trastuzumab or other HER2-targeted agents have as high as a 27% risk of cardiotoxicity and subsequent cardiac events [19]. Treatment with fluoropyrimidines has been shown to cause a multitude of cardiac complications including premature atherosclerosis and AMI [20–24]. Atherosclerosis, AMI, heart failure, and cardiac arrest have been associated with proteasome inhibitors, interferon, and interleukin-2 (IL-2) [25–27].

2.4. Heavy alcohol consumption

While several studies have indicated that moderate alcohol consumption is associated with a reduction in cardiovascular mortality, heavy alcohol consumption has been shown to have increased risk of atherosclerosis and mortality related to CVD. A prospective study over 8 years demonstrated men who consumed greater than 6 alcoholic drinks per day (or greater than 60 g of alcohol per day) were at higher risk for sudden cardiac death. This study also found that men with no

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