ABSTRACT

Worldwide, cardiovascular disease (CVD) is the largest single cause of death among women, accounting for 33% of all deaths. In many countries, more women than men die every year of CVD, highlighting the unique aspects of risk factor management of CVD in women. Major depressive disorder is also an illness that affects women more often than men; thus, cardiovascular conditions among patients with chronic mental illness such as depression represent an additional vulnerability and a compounded burden of illness for women. Clinical and hormonal changes that occur during pregnancy and the postmenopausal period also represent life events that require specific attention and represent a time of heightened vulnerability for both mood disorders and CVD risk. This article addresses the role of gender in risk stratification and in the responsiveness to preventive interventions for CVD in women with depression. Moreover, it reviews existing evidence on sex hormones as modulators of biomarkers and clinical measures of CVD in depressed patients.

FOCUS POINTS

• Women are more likely to suffer from major depressive disorder (MDD) than men; cardiovascular disease (CVD) is the largest single cause of death among women, accounting for 33% of all deaths.
• The heightened prevalence of MDD and CVD result in a compounded burden of illness among women; nonetheless, few studies have explored the potential role of gender differences for the development and management of CVD among depressed patients.
• The prevalence of CVD in MDD female patients appears to be modulated by hormone changes and different inflammatory response across the reproductive life cycle.

INTRODUCTION

Coronary heart disease (CHD), stroke, and peripheral vascular disease all contribute to overall mortality rates attributed to cardiovascular disease (CVD); despite significant efforts in disease prevention, CVD remains a major health concern in the developed world. It kills one in every five individuals and remains the leading cause of death in the United States and most developed western countries. CVD is also the largest single cause of death among women. In many countries, including the US, more women than men die every year of CVD. While most of the attention remains focused on more “traditional” female diseases such as breast cancer, many more women die from CVD than from breast cancer (1 in 2.6 versus 1 in 30, respectively).
Cardiovascular Disease in Women With Depression: One More Thing to Worry About

Major depressive disorder (MDD) is more commonly diagnosed in women. The occurrence of cardiovascular events in patients with chronic mental illness such as depression may, therefore, represent a compounded burden for women both in terms of disease prevalence and access to treatment. Gender seems not only to predispose women with depression to the development of CVD, but also to influence the occurrence of MDD in women with heart disease. For example, recent data suggest that young women may be at particularly high risk for depression after an acute myocardial infarction.

Overall, patients with MDD die earlier than those without mood disorders from a variety of physical illnesses, and mortality data among patients with mood disorders from as early as 1916 have documented this increase. A 4-decade study found excess mortality for manic and depressed patients of both genders, with the increase in mortality being most prominent in the first 10 years post admission due to a mood episode. A population-based study of the specific mortality ratios (SMRs) for patients with MDD or bipolar disorder from 1973–1995 found that SMRs for all natural causes of death were 1.9 for males and 2.1 for females with bipolar disorder, and 1.5 and 1.6 for MDD, respectively. A meta-analysis that examined excess mortality in MDD found an increased relative risk for depressed subjects to die compared to non-depressed subjects (1.81, 95% CI: 1.58–2.07). A large component of this increased mortality risk is attributed to CVD. Among women with MDD, CVD is responsible for more deaths than suicide. Existing data suggest that the pathophysiology of the mood disorders and its contribution to the relative risk of cardiovascular events and heart failure may be affected by gender, which might be of potential relevance for the prevention, diagnosis, and therapy of these conditions.

METABOLIC SYNDROME IN WOMEN WITH MDD

A partial explanation for increased CVD in women in general and in particular among women with mood disorders is the heightened vulnerability in this population for the development of metabolic syndrome (MeS). MeS is defined by a cluster of risk factors that ultimately contribute to CHD. By definition, MeS requires the presence of any three of the following five criteria: central obesity (waist circumference >102 cm >40 in) in men, >88 cm >35 in) in women); elevated triglycerides (>150 mg/dL >1.7 mmol/L) or specific treatment for this lipid abnormality); raised blood pressure (BP; systolic BP >130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension); raised fasting glucose (>100 mg/dL >5.6 mmol/L) or treatment for type 2 diabetes); and reduced high density lipoprotein (HDL) cholesterol (<40 mg/dL <1.03 mmol/L) in males, <50 mg/dL <1.3 mmol/L) in females or specific treatment for this lipid abnormality). People with MeS are twice as likely to die from, and three times as likely to suffer, a heart attack or stroke. They have up to a nine-fold greater risk of developing type 2 diabetes, compared with people without the syndrome. Given that up to 80% of the 200 million people with diabetes globally will possibly die of CHD, MeS and diabetes now rank ahead of HIV/AIDS in worldwide morbidity and mortality.

Approximately 40% of the adult population in the US meets diagnostic criteria for MeS. A closer look at the National Health and Nutrition Examination (NHANES) III data that was obtained between 1984–1998, compared to the NHANES 1999–2000 results, reveals a greater increase in MeS prevalence in women. Young women (20–39 years of age) seem especially vulnerable, with a 78% increase in prevalence, compared to a non-significant 5% increase in men in this age group. Data on 728 women from the Women’s Ischemic Syndrome Evaluation (WISE) study showed that MeS was strongly associated with angiographic coronary artery disease and conferred an approximate two-fold adjusted risk of death and major adverse cardiac events.

In the Atherosclerosis Risk in Communities study, a total of 12,809 individuals who did not have diabetes or CVD at baseline were followed for an average of 11 years. Men and women with MeS were 1.5–2.0 times more likely to develop CHD than individuals who did not have MeS after adjustment for age, smoking status, low-density lipoprotein cholesterol, and race. In addition, the risk of CHD associated with the MeS was significantly higher in women (crude hazard ratios [HRs]=2.55) than in men (HRs=1.51).

In the San Antonio Heart Study, the cardiovascular mortality risk in subjects who had MeS was also shown to be significantly higher in women than in men, although the gender differences seen in cardiovascular mortality were only significant in individuals who had both MeS and type 2 diabetes. This association between type 2 diabetes and fatal CHD was also examined in a recent meta-analysis that showed a relative higher risk in women compared to men. The subgroup analysis of two recently published meta-analyses also indicate that the MeS might be a stronger risk factor for CVD in women than
in men (relative risk=2.10 vs. 1.57,22 and 2.63 vs. 1.98,21 respectively).

Many of the physical illnesses linked to MeS occur at high rates in patients with mood disorders and may represent the expression of overlapping pathophysiology linking these illnesses. The association between MeS and mood disorders, however, remains controversial due to conflicting data.24,25 These discrepancies might be due to differences in methodology (longitudinal vs. cross-sectional), or type of population studied (age, presence or absence of associated cardiovascular risk factors, history of MDD). A potential confounder appears to be the role of gender differences. While the majority of studies addressing the association between mood disorders and MeS indicated a relationship between the two conditions, those that were unable to find a correlation between the two conditions did find a relationship between women with mood disorders and MeS when populations were divided by gender.24,25

This highlights the need to explore the potential role of gender differences for the development and management of CVD among depressed patients and to target female sub-populations during periods of heightened vulnerability for both CVD and MDD (eg, the menopausal transition).26,27

THE CONTRIBUTION OF OBESITY TO CVD IN WOMEN WITH MDD

A key variable linking mood disorders with CVD is obesity. Obesity is associated with increased risk of all-cause mortality and, in the general population, obesity and its associated metabolic and cardiovascular complications represent a significant contribution to premature death.28,29 This relationship is especially relevant to the field of mental health. People with mood disorders are at higher risk for obesity in part due to a complex interplay of factors that include unhealthy lifestyle choices, reduced energy expenditure and increase in consumption of palatable energy-dense foods, unwanted effects of pharmacotherapy, and, ultimately, poorly understood biologic factors.

The amount of weight gain in patients with a mood disorder may not be the only factor linked to an increase in morbidity from obesity-related diseases; another factor may be the increased amount of centrally deposited adipose tissue. Abdominal fat distribution consists of two discrete depots, subcutaneous adipose tissue (SAT) and visceral (intra-abdominal) adipose tissue (VAT).

These patterns of body fat distribution predict CVD better than total body fat volume.30,31 A measure of VAT, the waist to hip ratio, is positively associated with increased blood pressure, increased triglycerides, and decreased HDL cholesterol.32 This association is of particular relevance for women with mood disorders as a recent study that investigated this relationship in premenopausal women showed that the depression was associated with VAT, not SAT.33 It has been speculated that these findings may, in part, explain the association between depression and CVD in this population as the reduced tendency to accumulate fat within the intra-abdominal sites may be one of the primary metabolic differences underlying the reduced risk of cardiovascular disease, metabolic syndrome, and diabetes in women.34 Normally, premenopausal women more frequently develop peripheral obesity with SAT, whereas men and postmenopausal women are more prone to VAT. After menopause, concentrations of lipoproteins as well as body fat distribution shifts to a more male pattern. Postmenopausal women have an increased tendency of visceral fat deposition, which by virtue of its proinflammatory and prothrombotic properties, contribute to their risk of developing MeS and CVD.35

THE ROLE OF INFLAMMATION

Women are more susceptible than men to obesity in general; presently, 2 million more women than men have a body mass index >30.36 Obesity predisposes individuals to an increased risk of developing many diseases, including atherosclerosis, diabetes, non-alcoholic fatty liver disease, certain cancers, and immune-mediated disorders such as asthma.37-39 Part of this increased vulnerability is related to the ability of adipose tissue to function as an endocrine organ and secrete a wide range of hormones. Among the soluble mediators derived from adipocytes (fat cells) are leptin, adiponectin, and resistin, all of which are considered to play a role in the regulation of energy metabolism.40-42 Obesity is also associated with a chronic inflammatory response characterized by abnormal cytokine and adipokine production, increased synthesis of acute-phase reactants, and the activation of pro-inflammatory signaling pathways. Inflammation plays an essential role in the development of insulin resistance and type 2 diabetes, the initiation and progression of atherosclerotic lesions, and plaque disruption.43 Mood disorders are also associated with the production of pro-inflammatory cytokines that influence CVD, and some studies suggest that depression pro-
motes an inflammatory process. The most compelling evidence of this derives from studies that have ameliorated depressive symptoms through psychotherapy and found corresponding declines in the magnitude of inflammation markers.\textsuperscript{44} Conversely, inflammatory processes contribute to depression and exposure to inflammatory mediators produces a constellation of behaviors (eg, hyposomnia, anhedonia, anorexia) that resemble depressive symptoms.\textsuperscript{45,46} Existing literature links mood disorders and inflammatory markers; several cytokines that are elevated in individuals with MDD and bipolar disorder, including IL-6 and C-reactive protein (CRP), predict cardiac morbidity and mortality,\textsuperscript{47,48} while an association between adiposity and elevated II-6 and CRP levels has been suggested in clinically depressed individuals.\textsuperscript{49} Woman seem especially vulnerable to the risks posed by inflammation. In an analysis of women participating in the Nurses’ Health Study, high levels of II-6, tumor necrosis factor-\textgreek{a}, and CRP were significantly related to an increased risk of CHD.\textsuperscript{50} These findings supported the results from the Women’s Health Initiative study, demonstrating white cell count and CRP as the strongest predictors for cardiovascular morbidity and mortality in postmenopausal women.\textsuperscript{51} The combination of increased central obesity and chronic low-grade inflammation appears to be a mechanism for the pathogenesis of CVD.\textsuperscript{52}

Variables other than weight also play a role in inflammation in women. Sex steroids may influence inflammatory processes and hence modify cardiovascular risk. Raised levels of CRP, homocysteine, lipoprotein(a) (Lp-a), and IL-6 are each independently associated with increased risk for cardiovascular events in women. While changes in these parameters across the menopausal transition cannot clearly be attributed solely to hormonal changes, endogenous sex steroid levels and exogenous hormone therapy seem to exert a modulatory effect. Elevations of the amino acid homocysteine, which is associated with arterial and venous thromboembolic disease, and Lp-a, a known independent risk factor for the development of atherosclerosis, occur with age and/or menopause,\textsuperscript{53,54} while CRP and IL-6 appear to be influenced by endogenous sex steroid levels and exogenous hormone therapy.\textsuperscript{55,56}

**PREVENTION**

It was noted with the recently updated guidelines on prevention of CHD in women that healthcare professionals should focus on women’s lifetime heart disease risk and not just on short-term risk.\textsuperscript{2} The guidelines emphasized that prevalence of CHD in women is such that nearly all women should be considered at risk for atherosclerosis. Prevention of CVD is paramount to the health of women and even modest control can have significant impact. Fortunately, most CVD in women is preventable, if recognized. Even the presence of a single risk factor at 50 years of age is associated with a substantially increased lifetime absolute risk for CVD and shorter duration of survival.\textsuperscript{57} With few exceptions, such as the use of aspirin for primary prevention of heart disease in women >65 years of age,\textsuperscript{58} recommendations to prevent CVD in women do not differ from men.\textsuperscript{2} However, there are certain circumstances in which prevention strategies or interventions should be individualized.

Hormone replacement therapy (HRT) is not recommended for either primary or secondary prevention of CVD, particularly in women in their late postmenopausal years.\textsuperscript{59} Estrogen deficiency leads to an unfavorable lipid profile,\textsuperscript{60} which until recently had been considered the main pathologic phenomenon responsible for development of atherosclerosis and CHD. However, improvement in lipid profile with HRT does not reduce cardiac disease events in clinical studies.\textsuperscript{61,62} It remains controversial whether different estrogen therapies would offer a better risks/benefit ratio when administered via different pathways or to younger versus older sub-populations of menopausal women.\textsuperscript{62}

The efficacy of non-pharmacologically based treatments in women also needs further evaluation. Data suggest that women with CVD respond differently than men to psychological treatments. Subgroup analyses of the Enhancing Recovery in Coronary Heart Disease Patients trial showed a significant treatment by sex interaction on cardiovascular outcomes, suggesting a protective effect of cognitive-behavioral therapy in men, but a tendency for harm in women.\textsuperscript{63} These results mirrored those of an earlier study, the Montreal Heart Attack Readjustment Trial (M-HART), which tested the effect of a nurse-based psychosocial support intervention at home for distressed patients after myocardial infarction.\textsuperscript{64} The M-HART program had no overall impact on cardiac or all-cause mortality over the year. However, separate preplanned comparisons in men and women revealed two times the odds of cardiac and all-cause mortality in treated women compared with control women, while there was no impact in men. Altogether, these data suggest that women and men respond differently to psychological interventions and highlight the importance of performing gender-specific analyses. At
the very least, gender-based stratification should be better planned in future studies to allow sufficient power to examine gender-related differences. A more targeted emphasis could also be placed on prevention programs based on gender. In a US study designed to examine the extent to which modifiable lifestyle behaviors are associated with the risk of having MeS, MeS was associated with physical inactivity in overweight men and in normal weight and overweight women, suggesting a high protective value of physical exercise in women.

Gender biases in the diagnosis and management of women with CVD also plays a role in the outcome of this illness, and this is compounded by the stigma associated with mental illness. During the past several decades, CVD mortality has markedly declined in the US, from >50% to approximately 36% as the underlying cause of death. Recent data suggest that the decline is largely due to improved diagnosis and treatment rather than to major successes in primary prevention. In contrast, patients with severe mental illnesses, lose ≥25 years of life expectancy, with the majority of the excess premature deaths due to CVD.

There is now a sufficient consensus that depression is a risk factor for CHD as well as an important prognostic factor in cardiac patients. Nonetheless, <50% of depressed medical patients are recognized by their physicians, and recognition has only mildly increased in the last 10 years. During an admission for acute myocardial infarction, <15% of patients with depression are identified, and evaluation and treatment of depression continue to be mostly ignored during routine cardiac care.

**CONCLUSION**

Knowledge of the unique aspects associated with the management and occurrence of CVD in women has improved significantly in the last few years, and there is now acknowledgement that gender is a confounder that needs to be addressed appropriately (Figure). The additional risk conferred by MDD both to CVD risk and its impact on long-term outcome also needs to play a role in risk stratification and management. This way, we may hope to decrease the mortality attributed to this illness in women.

**REFERENCES**


