Association between metabolic syndrome, hypertension, and chronic depression: a postmenopausal women prevention study

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ABSTRACT

Background. Chronic depression (CD) is common among postmenopausal women and is associated with an increased risk of cardiovascular disease (CVD). The diagnosis of CD is a challenging problem in clinical practice which is vastly underdiagnosed. CD detection in postmenopausal women with metabolic syndrome (MetS) or hypertension is necessary for CVD prevention. Our study aims to assess the prevalence of CD in postmenopausal women and the relationship between CD and MetS or hypertension. Results. The rate of CD was significantly higher among postmenopausal women with MetS compared with the control group [18% *versus* 8%; Odds ratio (OR) 2.2, P<0.007]. The CD rate was significantly higher among women with MetS and hypertension (21% *versus* 8%; OR 2.7, P<0.0000). The rate of CD was similar between women with MetS and women with hypertension, 18% *versus* 21%; OR 0.8, P<0.44) and between women with metabolic cardiomyopathy and hypertensive cardiomyopathy (10% *versus* 8%; OR 1.1, P<0.65). Conclusions. There is a relationship between MetS and CD, which is stronger when compared to women with hypertension. There is a need to improve the diagnosis of CD in postmenopausal women with MetS or hypertension as unrecognized and untreated CD is associated with a poor outcome.

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Introduction

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, including central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol which increases the risk of cardiovascular events.[1] Chronic depression (CD) is the most common psychiatric disorder in the world and in primary healthcare settings.[2,3] Unrecognized and untreated depression is associated with a poor outcome even with treated chronic diseases when co-existing.[4] CD is a common disorder in cardiovascular patients with a prevalence of 20% to 45%, which is much more frequent than in the general population.[5] The CD that was investigated in this study is different from psychotic depression and depression with a coexisting diagnosis of personality disorder. The morbidity and mortality of cardiovascular disease (CVD) are exceedingly high worldwide, and epidemiological studies have confirmed high co-morbidities when chronic depression and CVD co-exist. CD and CVD are bidirectionally related conditions and often co-exist and the underlying mechanisms are complex and multifactorial. Many women present with CD during their life, and depressive symptoms have been considered a non-traditional risk factor for CVD in the general population.[6] The early diagnosis of CD is a challenging problem in clinical practice. When diagnosed in postmenopausal

women with MetS, it is important to treat CD to improve their quality of life. Our study aims to assess the prevalence of CD in postmenopausal women with MetS and/or hypertension.

Materials and Methods

We enrolled 100 consecutive postmenopausal women with MetS and 500 postmenopausal women with hypertension aged between 48 and 68 years who were referred to our Heart Station for cardiac evaluation. The control group consists of 500 consecutive normotensive women without MetS, aged between 48 and 68 years. The demographics including age, height, weight, body mass index (BMI), and symptom duration were collected. All women underwent electrocardiographic and echocardiographic evaluation. Exclusion criteria were thyroid disorders, other cardiovascular diseases, malignancies, neurological disabilities, and psychotic disorders. Informed consent was obtained from all participants in the study.

A detailed personal history of metabolic and CVD was collected along with anthropometric parameters such as measurements of body weight, height, and waist and hip circumferences. Weight and height were used to assess BMI; the ratio between weight in kilograms and height in squared meters. Obesity was defined as a BMI of 30 kg/m^2 or greater, according to the 2020 World Health Organization recommendations.[7] Blood pressure (BP) measurements were performed on the upper arm with a sphygmomanometer after at least 5 minutes of rest and the cuff involved 80% of the upper arm circumference. The average of three measurements was taken as the individuals' BP value. Hypertension was defined by the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Criteria.[8] MetS was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III definition. For this assessment, we need three or more of the following five criteria: waist circumference over 35 inches for women and more than 40 inches for men, blood pressure over 130/85 mmHg, fasting triglyceride level over 150 mg/dl, fasting HDL cholesterol level less than 50 mg/dl for women and 40 mg/dl for men and fasting blood sugar over 100 mg/dl.[1] CD recognition and assessment was performed for all women on therapy with anti-depressive treatment and cognitive behavior therapy associated with medications, according to National Institute for Health and Care Excellence (NICE) 2009 Guidelines, updated in 2022.[9] Transthoracic echocardiography was performed with the patient in the left lateral decubitus position, after 10 minutes of resting, with the exam table elevated by 30°. The exam was carried out with 3.5 MHz probes with an electrocardiogram trigger. An echo-doppler system equipped with a multifrequency transducer, Philips Epiq 7, Ultrasound System for Cardiology, Healthcare, Viale Sarca 235, Milan (Italy) was used. Normal values of the echocardiography parameters were established according to the American Society of Echocardiography. Cardiomyopathy diagnosis was formulated according to well-established criteria.[10-13]

Results

The rate of CD was significantly higher among postmenopausal women with MetS compared to the control group [18% *versus* 8%; Odds ratio (OR) 2.2, P<0.007] (Table 1). The CD rate was significantly higher among women with MetS and hypertension (21% *versus* 8%; OR 2.7, P<0.0000) (Table 2). The rate of CD was similar between women with MetS and women with hypertension, 18% *versus* 21%; OR 0.8, P<0.44**)** and between women with metabolic cardiomyopathy and hypertensive cardiomyopathy (10% *versus* 8%; OR 1.1, P<0.65) (Table 3). CD rate was significantly higher among women affected by metabolic cardiomyopathy than control (10% *versus* 0%; OR: 6.5, P<0.0000) (Table 1), and by hypertensive cardiomyopathy compared to control (8% *versus* 0%; OR: 2.1, P<0.0000) (Table 2).

Discussion

The main finding of our study is that CD is relatively common in postmenopausal women with MetS. Women with MetS have a twofold chance to be affected by CD than the general population, and hypertensive women have an almost triple chance. This information is relevant because the American Heart Association has endorsed CD as a non-traditional cardiac risk factor and recommends screening as part of routine practice.[14] Additionally, there is a lack of data linking CD treatment and cardiovascular outcomes.[15] Socio-economic status, personality, health behavior, and biological traits all contribute to the occurrence of CVD and cardiac events. It is well known that a significant number of women are affected by CD during their life, and depressive symptoms have been considered a relevant, emerging risk factor for CVD in the general population.[16-18]

Women seem to be more strongly affected by psychosocial stressors and CD related to CVD by direct and indirect effects of chronic stress compared to men. There are gender-specific differences in biological responses to mental stress in those involved in hypertension.[19] More evidence in understanding these differences within biological, psychosocial, and social determinants and pathways is essential for promoting

women's health. The relationship between CD and CVD is bidirectional and the underlying mechanisms are complex and multifactorial. The clear correlation that exists between CD and CVD is due to behavioral and biological risk factors, including sympathetic nervous system hyperactivity and impairment in hypothalamic-pituitary-adrenal function, chronic systemic inflammation, and modulation of cardiac autonomic control. These effects create a homeostatic imbalance between the sympathetic and parasympathetic systems with loss of heart rate variability in CD, sympathoadrenal activation, hypothalamic-pituitary-adrenal axis activation, immune system dysregulation resulting in a pro-inflammatory status, platelet activation, and endothelial dysfunction.[20] A likely common trigger factor for the association between CVD and CD is mental stress. Chronic stress shifts the homeostatic balance in the autonomic nervous system with increased sympathetic overdrive and decreased vagal tone, contributing to a pro-inflammatory status. Stress hormones and proinflammatory substances determine the synthesis of neurotoxic metabolites.[21,22] Inflammation is closely associated with endothelial dysfunction, a precursor of atherosclerosis and atherothrombosis. Endothelial dysfunction has been detected in CD, confirming the clinical relevance of vascular pathophysiology and psychiatric disorders.[23]

The CD is often unrecognized or undertreated in CVD patients, which leads to significant morbidities and even mortality.[24,25] It predisposes patients to these comorbidities through a number of mechanisms and their complex interactions, overall increased levels of inflammatory cytokines, a high prevalence of traditional CVD risk factors, side effects of pharmacotherapy, and relevant psychological stress. CD and CVD are linked through a shared genetic predisposition; data were assessed in the study and confirmed after adjustment for known environmental influences, particularly those related to socio-economic status, age, gender, smoking, education, age, and BMI.[26] The pathophysiological mechanisms underlying the link between MetS and CD need to be further investigated. However, MetS is often found among depressed patients with an unhealthy lifestyle, determining an imbalance of the stress system, that encloses the hypothalamus-pituitary-adrenal axis, the autonomic nervous system, the immune system, and platelet and endothelial function. Both MetS and CVD establish low-grade chronic inflammation with increased oxidative, neuronal and endothelium cell dysfunction. Based on currently available evidence, metabolic risk should be routinely assessed in depressed patients.

There is evidence that relevant exposure to chronic stressors in women, interpersonal stress responsiveness, and internalizing coping styles are associated with hypertension,[27] MetS, and high risk of CVD and/or CD through behavioral and pathophysiological mechanisms which hypothalamic-pituitary-adrenal

Table 1. Chronic depression in women with metabolic syndrome *versus* control.

	Metabolic syndrome	Control	Odds ratio	P-value
All women	100	500		
Women with CD	18 (18%)	45 (8%)	2.2	<0.007
Women with CD and MC	10 (10%)	0	6.5	<0.000

CD, chronic depression; MC, metabolic cardiomyopathy.

Table 2. Prevalence of chronic depression in women with hypertension *versus* control.

	Hypertension	Control	Odds ratio	P-value
All women	500	500		
Women with CD	107 (21%)	45 (8%)	2.7	<0.000
Women with CD and MC	43 (8%)	0	2.9	<0.000

CD, chronic depression; MC, metabolic cardiomyopathy.

Table 3. Chronic depression in women with metabolic syndrome *versus* hypertension.

	Metabolic syndrome	Hypertension	Odds ratio	P-value
All women	100	500		
Women with CD	18 (18%)	107 (21%)	0.8	<0.44
Women with CD and cardiomyopathy	10 (10%)	43 (8%)	1.1	<0.65

CD, chronic depression.

function dysregulation and autonomic nervous system imbalance appear to be specific for women.[28] Pharmacologic and psychotherapeutic interventions appear to be safe and effective at reducing depressive symptoms in patients with CVD and may impact cardiac outcomes.[29,30] We recommend routine screening of CD in cardiac patients for effective management and referral to a psychiatrist or care management program to deliver pharmacologic and psychotherapeutic treatments in this vulnerable population of postmenopausal women.

Limitations

This study has some limitations concerning CD diagnosis that we assessed in women on pharmacologic and/or psychotherapeutic for almost six months, likewise, the metabolic cardiomyopathy diagnosis was done following the same criteria adopted for the diagnosis of metabolic cardiomyopathy. However, the sample size is adequate, and measurements were obtained according to the standard protocols, and following the current guidelines.

Conclusions

This study showed a relationship between MetS and CD in postmenopausal women, which is even higher in hypertension. However, the relationship was similar between women with metabolic or hypertensive cardiomyopathy. An intervention is needed to improve the diagnosis of CD in postmenopausal women, more so in patients with MetS and/or hypertension because unrecognized and untreated CD is associated with a poor cardiovascular outcome.

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