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Age-Related Cardiovascular Diseases in Women: The "48-Syndrome"

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are a leading cause of mortality globally, with significant gender differences in incidence and outcomes. While men experience a higher incidence, women, especially those undergoing menopausal transition, exhibit greater CVD-related mortality rates. The following opinion report outlines a trend in CVD risk among women aged 48 years, a crucial point of time associated with perimenopausal changes. Despite presenting symptoms such as severe shortness of breath (SOB) and ischemic chest pain, standard diagnostic tests including electrocardiogram (ECG), and coronary angiogram (CA) often yield normal results suggesting a need for improved diagnostic approaches.

Discussion: Hormonal fluctuations: particularly relating estrogen, increase the risk of atherosclerosis, arterial stiffness, and dyslipidemia. Additionally, alterations in lipid metabolism, weight gain, central obesity, and insulin resistance during multiple stages of menopause further exacerbate cardiovascular risks. Inflammation and endothelial dysfunction driven by the variation of estrogen concentrations contribute to vascular abnormalities, while psychological health declines: such as stress and anxiety, may aggravate these conditions.

Conclusion: This unique age-specific trend of increased CVD risk at age 48 years in women has been termed the "48-Syndrome." This highlights the importance of early detection and intervention for middle-aged women. Understanding this age-related phenomenon provides a foundation for developing targeted prevention strategies, improving cardiovascular health, and reducing mortality rates in women during this critical life stage.

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Introduction

Cardiovascular diseases (CVDs) are a leading cause of mortality worldwide, accounting for an estimated 20.5 million deaths annually [1]. Gender distribution analysis indicates that men have a higher incidence of CVDs compared to women [2]. However, despite a lower prevalence of CVDs among women, multiple studies have demonstrated that the female population experience higher rates of mortality due to CVDs: 16 folds compared to breast cancer [3,4]. Notably, studies have found that menopausal transition period, also known as perimenopausal transition is a significant phase of elevated cardiovascular risk in women [5,6].

A study conducted in Sri Lanka reveals that the mean age at menopause is between 49 and 51 years [7]. Menopause is the permanent halt of the menstrual cycle, resulting in oocyte depletion and the loss of gonadal steroid production. The process of menopause can be divided into three main stages: perimenopause, menopause, and post-menopause. Perimenopause is a transitional stage that precedes menopause, marked by vast hormonal variations, irregular menstruation patterns, continuous loss of oocytes, and diminished sensitivity to gonadal steroid feedback [8]. Perimenopause usually starts around the age of 47-48 and lasts four to eight years on average [9]. Perimenopausal changes are associated with several physiological and hormonal changes that contribute to an increased risk of CVD in women due to various factors.

The following report highlights an emerging trend in cardiovascular diseases (CVDs) among women specifically around the age of 48. This particular age group seems to be a crucial point where the risk of developing CVDs significantly increases, likely due to hormonal changes, lifestyle factors, and physiological aging processes. Cardiovascular health in women has been under-researched throughout, and focusing on this age group could help identify early risk factors and create targeted prevention strategies. This opinion report aims to improve understanding and provide evidence-based solutions for reducing cardiovascular risks in middle-aged women.

Discussion

Here we discuss a notable rise in females aged 48 to 49, who often present with progressive severe shortness of breath (SOB) associated with ischemic chest pain. Despite these alarming symptoms, this group frequently results normal findings on both resting and exercise electrocardiograms (ECG). Furthermore, invasive tests such as coronary angiography (CA) often reveal no abnormalities in coronary function or physiology, and troponin levels in these patients are typically within the normal range, excluding the diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA).

Therefore, this suggests a potential gap in current diagnostic methods, which may not adequately account for the metabolic health of this population. The following listed factors linking CVDs to middle-aged women justify the identification of the 48-Syndrome as a critical life stage where cardiovascular vulnerability is at its highest.

Estrogen Fluctuations

The estrogen hormone plays a key role in the cardiovascular system by promoting vasodilation, inflammation inhibition, and lipid profile regulation. Numerous studies have demonstrated the association between specific estrogen-mediated cardiovascular system activities and the mitigation of local oxidative stress (OS), which can lower reactive oxygen species (ROS) by the regulation of ROS enzyme production and enhancing ROS clearance [10,11]. Alterations in estrogen concentrations result in multiple changes in the vasculature leading to increased risk of atherosclerosis and arterial stiffness [12].

Additionally, estrogen also has a positive effect on lipoprotein profiles, lowering low-density lipoproteins (LDL) and raising high-density lipoproteins (HDL) [13]. Therefore, decreased estrogen levels lead to higher LDL and triglyceride levels while reducing HDL, which further contribute to the development of atherosclerosis.

Alterations in Lipid Metabolism

Hormonal changes during the menopausal transition lead to the emergence of various lipid metabolic disorders, including decreasing levels of estrogens and increasing levels of circulating androgens [14]. This is due to multiple mechanisms linked to CVDs have been suggested to be directly regulated by estrogen, particularly in the liver. Estrogen activity in various other organs may also indirectly influence the process of which estrogen affects plasma lipid responses and liver lipid metabolism [15]. Body fat mass, fat-free mass, fatty acid metabolism, and other elements of energy metabolism, including baseline metabolic ratio, adiposity, and obesity, are all impacted by dysregulation of lipid metabolism [14].

Weight Gain and Central Obesity

Perimenopausal transition is also associated with weight gain and increase in body fat, particularly visceral fat, which is linked to cardiovascular risks [16]. The development of obesity in perimenopausal women has been linked to hormonal changes brought on by menopause, such as hypoestrogenaemia, hypergonadotropinemia, growth hormone deficiency, leptin resistance, and long-term stress that affects the hypothalamic-pituitary-adrenal axis. The above-mentioned combination of hormonal fluctuations causes metabolic alterations that increase the likelihood of developing metabolic syndrome, which greatly increases the risk of CVDs [17]. Weight gain and central obesity may introduce symptoms such as SOB progressively.

Insulin Resistance

The decline in estrogen also significantly impacts the glucose metabolism. Insulin resistance is proved to be a major factor in the onset on menopause [18]. Lower estrogen levels during menopause can reduce insulin sensitivity, increasing the risk of developing type 2 diabetes, which imposes a greater risk in the development of CVDs [19]. A study conducted in China suggests that an overwhelming majority of the population undergoing perimenopausal syndrome reports varying incidences of dyslipidemia, hypertension, overweight or obesity and non-alcoholic fatty liver disease (NAFLD): all of factors which contribute to CVDs [20].

Inflammation and Endothelial Dysfunction

Multiple sources of existing literature prove that menopause-related hormonal changes are directly linked with increased inflammatory responses and endothelial dysfunction, both of which are critical in the development of CVDs [21-23]. This is caused due to the elevated levels of key proinflammatory cytokines IL-6 and TNF-alpha produced during multiple menopausal stages [23]. The rise of pro-inflammatory markers are associated with the sudden drop in estrogen concentration, and this leads to chronic low-grade inflammation, which is a major contributor in the development of atherosclerosis [24]. The endothelium progressively become less functional during the menopause, leading to reduced blood flow, heightened vascular stiffness, and an increased risk of clot formation [22]. Coincidingly, other sources of literature suggests a significant rise of neurodegenerative disease in women of peri-menopausal women [25].

Psychological Impact

Furthermore, physiological changes, psychosocial and lifestyle factors during the menopausal transition may contribute to cardiovascular risks. Menopausal women frequently experience psychological anguish, which is linked to vasomotor symptoms [26]. Vasomotor symptoms cause fatigue, poor sleep quality, and low self-esteem, all of which can contribute to low mood; on the other hand, excessive anxiety or depression can cause unfavorable perceptions of vasomotor symptoms and the use of unhealthy coping mechanisms such as poor diet, lack of physical activity, and smoking, all of which are risk factors for CVDs [27].

Recommendations

It is advised to introduce early screening for middle-aged women, emphasizing metabolic health evaluations such as lipid profiles to mitigate cardiovascular risks associated with the "48-Syndrome." Diagnostic methods should be refined to identify underlying cardiovascular issues stemming from hormonal and metabolic shifts. Lifestyle modifications related to diet, physical activity, and stress management should be promoted, alongside mental health support. Hormone replacement therapy may help alleviate estrogen-related cardiovascular risks. However, this treatment strategy should be approached individually [28,29].

Conclusion

In conclusion, a significant age-related risk factor is highlighted by the trend of increased CVD incidence and mortality among women aged at 48 years. This age-specific phenomenon has been dubbed the "48-Syndrome" due to the unique pattern that is seen at this particular age, emphasizing the value of early detection and treatment. Additionally, this population may be metabolically unhealthy, with contributing factors such as insulin resistance, obesity, and dyslipidemia playing a role in their cardiovascular risks. Therefore, by introducing the term "48-Syndrome" to describe this phenomenon, we hope to raise awareness of a particularly vulnerable age group and pave the way for additional investigation into the underlying reasons and risk factors related to cardiovascular health in women during this critical life stage. By addressing this syndrome, prevention and treatment plans can become more individualized and age-specific, which will eventually benefit women who are at risk of CVDs.

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