**Introduction**

Menopause is the time point when a woman did not have her menstrual cycle in the last twelve months. In the years preceding menopause, an individual can experience irregular flow, changes in the cycles, and hot flashes, also called the perimenopausal phase. The mean age of the natural menopause of women across the globe is between the age of 45 and 53 years. This age range is 48.1-48.7, 48.1-49.4, 49.8-52.8, 50.0-51.1, 45.9-48.6, 46.9-47.8, and 48.8-49.4 years in Africa, Asia, Australia, Europe, Latin America, Middle East, and the USA, respectively (1).

The commonly observed menopausal symptoms are hot flashes, excessive sweating, difficulties in sleeping and waking up, depressive disorders, insomnia, irritability, anxiety, cognitive changes, forgetfulness, reduced libido, urogenital disorders, osteoporosis, and discomfort associated with muscles, bone, and joint system (Figure 1) (2).

Menopausal symptoms are common to all women but the prevalence can vary according to ethnicity and geographic location. There are several reports on the prevalence of these symptoms across continents (3) and in people from different sociodemographics (4-7). The menopausal episode can be a different experience and depends on the current health status of an individual, socioeconomic status, and personal history of the individual. Dr. Gerald Reaven first described the metabolic syndrome in 1988. He described it to be a constellation of physiological risk factors, including increased blood pressure, insulin resistance, atherogenic dyslipidemia, and visceral adiposity, all of which lead to cardiovascular disorders (8, 9). Metabolic syndrome is more prevalent in women than in men in the US, and more than 50 % women are of 60 years or older (10, 11), and this difference in prevalence is observed worldwide (12-16). Among all the metabolic syndromes, the most common one is central and abdominal obesity (17-19). Menopause predisposes a woman to metabolic dysfunctions, and various alterations occur in her body. Thus, postmenopausal metabolic syndrome is a highly common event in most women's lives as they get older. Many cross-sectional studies have reported that the risk of postmenopausal metabolic syndrome varies from 32.6% to 41.5% (20, 21), and a higher prevalence is reported in developing countries like those located in Asia (22). However, a limited body of research has been performed on postmenopausal metabolic syndrome and its effective treatment and management after the detection of the disorder. A review-based study will help researchers to detect the syndrome in postmenopausal patients and properly manage the disease.

This review discusses the most common
Postmenopausal metabolic syndrome, their detection, and management for overall improvement in the lifespan and quality of life of an individual.

Methods
For writing the review no particular structure was followed for searching research articles based on metabolic syndromes and their occurrence in postmenopausal women. Articles were mainly retrieved from PubMed and ScienceDirect databases, and the manual search of full-text papers with keywords such as postmenopausal metabolic disorders, hormone replacement therapy, estrogen, cardiovascular disease after menopause, cancer, metabolic errors. The studies that reported cases of metabolic syndrome after menopause, diagnosis of the disorders, and management of postmenopausal symptoms have been summarized in this review. No inclusion criterion was preassigned for writing the review, and the review did not consider any barrier to religion, region, time, or language. Moreover, all the study designs reporting about postmenopausal metabolic syndrome have been included in the study.

Results
The findings from the literature review have been reported as the common metabolic syndromes after menopause, cancer, and menopause, as well as early detection of postmenopausal metabolic syndrome and its treatment and management.

Common Metabolic Syndromes After Menopause
The characteristics of menopausal metabolic syndromes are as follows:
- Increased gluconeogenesis
- Overweight
- Increase in cardiovascular risk
- Obesity
- Alteration in lipid profile
- Hyperinsulinemia

Factors facilitating the onset of postmenopausal metabolic syndromes are shown in Figure 2 (23, 24).

Cardiovascular Diseases
Cardiovascular Disease (CVD) is one of the primary causes of death among men and women with women at a higher risk of CVD after the age of 50 and reaching a similar rate of incidence by 70 years of age. One of the main reasons could be substantial metabolic changes occurring in women's bodies in the transition from pre- to post-menopause. Myocardial infarction and atherosclerotic disease are not common in premenopausal women and only occur at a later age. However, the increased risk of CVD after menopause is controversial (25). Estrogen deficiency may increase the risk of CVD in women who develop certain metabolic syndrome postmenopause. Carotid intima-media thickness (CIMT) is a strong predictor of the risk of developing CVD (26) and a study of CIMT shows the risk of CVD in 45 % postmenopausal women which is clinically significant (27). Postmenopausal women have a higher incidence of aortic calcification, and the extent of calcification increases with increasing years of post-menstruation (28, 29). The calcium deposit in the coronary artery of post-menstrual women also increases, indicating that
atherosclerosis has a strong relationship with menopause. The prevalence of metabolic syndromes, especially lipid metabolism and estrogen deficiency, may also lead to an increased CVD risk in postmenopausal women. Nearly 50% of the cardiovascular problems in women are attributed to metabolic syndromes which are prevalent at a higher age (30).

**Disorders in Lipid Metabolism**

Dyslipidemia is a common occurrence in menopause which is characterized by an increased low-density lipoprotein (LDL) level and a decreased high-density lipoprotein (HDL) level. The healthy women study revealed that comparing premenopause and menstruating women of the same age group, the premenopause women had an increased level of LDL and total cholesterol and decreased level of HDL and HDL, than the menstruating women (31). There is a decrease in the HDL antiatherogenic effect in premenopausal and postmenopausal women due to changes in the lipoprotein subclass profile. These changes impact the cardiovascular condition and may also lead to atherosclerosis (23).

**Disorders in Carbohydrate Metabolism and Diabetes**

Carbohydrate metabolism disorders in the form of non-insulin dependence and menopause have many common symptoms such as significant weight gain or weight loss, increase in thirst, increase in appetite, irritability, recurrent urogenital inflammations, blurred vision, fatigue weakness, and the like. The estrogen deficiency in the body after menopause may be a reason for the development of diabetes, and aging is also related to the development of an increasing risk of non-insulin-dependent type 2 diabetes (T2D). Lifestyle and medications are also risk factors for the development of diabetes. Calcium deficiency, which is commonly observed in postmenopausal women, and impairment in vitamin D metabolism may lead to an increased risk of both T1D and T2D (32). The concentration of sex hormone-binding globulin (SHBG) is inversely related to insulin resistance, and its low level indicates the risk of developing T2D (24). A high level of testosterone is positively related to the development of T2D. Hormonal therapies help in the prevention of the onset of T2D.

**Polycystic Ovarian Syndrome**

Polycystic ovarian syndrome (PCOS) identified in an individual in their reproductive stage also persists after menopause. However, postmenopausal women having PCOS have a higher index of free androgens and lower follicle-stimulating hormone and SHBG than those without PCOS. Postmenopausal women with PCOS had hypothyroidism, reported more hair growth in unwanted areas and areas where generally hair growth does not occur, and had less frequent climacteric symptoms than those without PCOS (33). Glucose tolerance and chronic inflammations that were observed in PCOS patients before menopause persisted after menopause and thus PCOS seemed to be an independent factor. Postmenopausal PCOS women have hyperinsulinemia, higher C-reactive protein (CRP), higher androgen, and higher free androgen indices (34). Menopausal women with PCOS are more prone to develop CVDs, diabetes, and hypertension and have a higher triglyceride level and a higher incidence of stroke, myocardial infarction, and cancer. Menopausal women have a higher mortality rate than normal postmenopausal women (35).

**Thyroidism**

There is no direct evidence of the relationship between menopause and thyroid dysfunction, but the clinical representation of some thyroid diseases may get modified, including the autoimmune ones. However, with age, there are some changes observed in thyroid physiology and function; they include a reduction in the level of free thyroxine, a decline in the uptake of thyroid iodine, a decrease in the catabolism of free thyroxine, a reduction in free triiodothyronine synthesis, and an increase in the level of triiodothyronine, and the level of the thyroid-stimulating hormone remains within range (mostly being on the upper side) (36). The conditions of coronary atherosclerosis and osteoporosis that appear after menopause may get aggravated due to hyperthyroidism or hypothyroidism (37). The symptoms of the manifestation of menopause and thyroid-related disorders may be similar, including hot flashes, palpitations, sweating, irritability, mood swings, insomnia, weight gain, hair fragility, constipation, and the like.

**Cancer and Menopause**

Cancer and postmenopausal stage are generally not related to each other. However, the chance of a woman developing cancer increases with age, and women with cancer may reach menopause earlier due to damage caused to the ovaries. The most common cause of postmenopausal bleeding has been reported to be endometrial cancer. A meta-analysis comprising 129 studies which included more than 40 000 women from Asia, North America, and Europe (1977-2017) revealed that around 9% of women who were diagnosed with endometrial cancer had endometrial bleeding (North America [5%] and Western Europe [13%]) (38). Women who have delayed menopause (after 55 years) and who start menstruating early (before 12 years) tend to have a greater risk of developing uterine, ovarian, and breast cancer (BC) (39, 40). The risk of developing BC increases with increased exposure to estrogen, whereas normally both the levels of estrogen and progesterone show a sharp decrease around menopause. The risk of ovarian cancer increases with delayed menopause due to too
individuals develop sarcopenia, and a study demonstrated a prevalence of 22.8% (51). More than 40% of obese muscle mass is also related to metabolic syndrome with T2D by 13% (50). Sarcopenia or the loss of skeletal muscle strength decreases the risk of developing metabolic syndrome. The high-to-medium level of muscular strength decreases the risk of developing metabolic syndrome. The CIMT test performed to determine the risk of developing metabolic syndrome. An increased resting heart rate of 10 beats per minute increases the risk of metabolic syndrome by 28% (48). CIMT test performed to determine the formation of plaques in arterial walls that supply blood to the brain can also determine the risks of metabolic syndromes.

Early Detection of Metabolic Syndromes in Postmenopausal Women for Effective Treatment

Metabolic syndromes that are undiagnosed and untreated may affect the length and quality of life of women. Early detection of the risks of metabolic syndromes is thus a priority of clinicians and researchers for improving the quality of life of patients. A woman with metabolic syndrome is generally diagnosed from the presence of three or more of these risk factors, including a waist circumference (WC) of more than 88 cm, triglyceride level of more than or equal to 150 mg/dL, level of HDL of less than 50 mg/dL, blood pressure of more than or equal to 130/85 mm Hg, and the fasting glucose level of more than 110 mg/dL (43). The risk factors of T2D are high blood pressure, high resting heart rate, low hip circumference, waist-to-hip, waist-to-height ratio, increased WC, triglyceride-glucose index, and high body mass index (BMI) (44, 45). Neck circumference has an association with the parameters of metabolic syndromes. An increase in circumference is positively related to WC, BMI, fasting blood glucose level, LDL, and total cholesterol but negatively related to HDL. People with increased neck circumference have a risk of developing hypertriglyceridemia (46). A cardiorespiratory fitness of a minimum of 8.39 metabolic equivalents is required to increase with an increase in ferritin (65). Researchers found a 40%-60% decreased risk of developing the two most common BC, namely, invasive ductal and lobular carcinoma (42).

Uric acid

The high level of circulating uric acid increases the risk of metabolic syndrome and the prevalence of T2D and nonalcoholic fatty liver disease (54).

Vitamin D

Low levels of vitamin D and increased risk of metabolic syndrome and hypertension are not associated. However, its low levels lead to a higher prevalence of PCOS, non-alcoholic fatty liver disease, higher WC, BMI, abdominal adiposity, T2D, and prediabetes (55-60).

Sodium

Patients with higher sodium levels have higher chances of developing metabolic syndrome than patients with low urinary/dietary or serum sodium (61).

Magnesium

It helps in the proper functioning of the cardiovascular and neurological systems. Low levels of magnesium lead to an increased risk of metabolic syndrome. A meta-analysis reported an OR of 0.7 for metabolic syndrome, and magnesium being associated to metabolic syndrome(62).

Amino Acids

Among the 20 essential and circulating amino acids in the human body, Ala, Val, Lys, Pro, Leu, Ile, His, Glu, Met, Trp, Tyr, and Phe, are the ones that have higher levels in patients with metabolic syndrome, while Gly, Ser, Asn, and Gln have lower levels in patients with metabolic syndrome (63).

Ferritin

This protein acts as a buffer against iron deficiency, and a high level of ferritin is an indirect marker of the body’s total stored iron. Ferritin is involved with the impaired metabolism of glucose and hypertension (64), and its high level increases the risk of metabolic syndrome (1.39), lower HDL (1.24), and higher WC (1.14) (53).

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**Eating and Nutritional Factors**

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**Bilirubin, Alanine Aminotransferase, and Gamma-glutamyl Transferase**

Alanine aminotransferase and a high level of bilirubin are good indicators of hepatic damage, and gamma-glutamyl transferase is a good indicator of metabolic syndrome (66). Many cross-sectional studies, however, confirmed that high levels of bilirubin can play a protective role on metabolic syndrome and its decreased level can increase the risk of T2D (67).

**n-3 Polynsaturated Fatty Acids**

A higher level of plasma/serum n-3 polyunsaturated fatty acids (PUFAs) reduces the risk of developing metabolic syndrome. However, the dietary intake of n-3 PUFAs or fish is not related to the low risk of developing metabolic syndrome (68).

**Fibroblast Growth Factor 21**

This signalling protein is involved in differentiation, the proliferation of cells, and metabolism. An increase in the level of fibroblast growth factor 21 (FGF21) is associated with an increased risk of metabolic syndrome (a 1.7 hazard ratio) and the incidence of T2D (a 1.35 hazard ratio) (69).

**Triglycerides**

Increased levels of non-fasting triglycerides (mainly in women) and total cholesterol (mainly in men) are linked to the increased risk of ischemic heart disease and myocardial infarction. Non-fasting triglycerides are associated with total mortality, but total cholesterol is not related to mortality (70).

**Testosterone and SHBG**

The levels of testosterone and SHBG are more important than estrogen in women belonging to the pre- and postmenopausal group for the assessment of the risk of metabolic syndrome. An increase in free testosterone is related to increased BMI and WC in postmenopause (71).

**Inflammatory, Anti-inflammatory, Pro-oxidant, and Antioxidant Parameters**

Pro-inflammatory cytokines (e.g., interleukin [IL]-6, tumor necrosis factor-alpha, and CRP), anti-inflammatory cytokines (e.g., IL-10), prothrombic factors (e.g., PAI-1), adipokines (e.g., lutein and adiponectin), and antioxidant markers (e.g., OxLDL and PON-1) are strong indicators of metabolic syndrome (72). The pro-inflammatory parameters are increased while anti-inflammatory parameters are decreased in the cases of metabolic syndrome. A high level of serum lutein reduces the risk of metabolic syndrome, and its high level is beneficial in cases of atherosclerosis. However, there is no association of lutein with adiposity, blood lipid, and blood pressure (73).

**Management of Postmenopausal Metabolic Disorders**

The key elements for the management of metabolic syndrome are increased physical activity, reduced weight (keeping BMI levels below 25 kg/m²), and diet modification for controlling blood pressure, lipid profile, and glycemic control of the body. Other pharmacological interventions such as hormone replacement therapy may occasionally be required as well, but the first-line treatment of menopausal metabolic abnormalities will always be lifestyle modifications with a healthy diet, along with moderate physical activity.

**Diet**

Prescribed food for the management of menopausal symptoms are as follows:

1. Cold-pressed oils (e.g., palm, virgin coconut, and olive oils) help in the regulation of estrogen production and the improvement of cardiovascular health (74).
2. Broccoli, kale, cabbage, and other green vegetables help in balancing estrogen levels and regulating blood pressure and heart health.
3. Food rich in omega-3 fatty acids facilitates hormone production and helps in the prevention of postpartum depression, menopausal problems, preeclampsia, and postmenopausal osteoporosis (75).
4. High-fiber food such as nuts, legumes/beans, and seeds help in balancing estrogen production (76).
5. Consumption of less than 5 g of salt/day, less than 300 mg of cholesterol/day, daily intake of 1 g calcium, and 800 IU vitamin D₃.
6. Adequate water of at least 8 glasses a day helps in replacing fluid loss from hot flushes and reduces bloating.

**Lifestyle Modifications**

- Giving up smoking and drinking alcohol (77).
- At least 30 minutes of moderate exercise and exercise for at least three days a week (78).
- Regular endurance exercise for improving insulin sensitivity irrespective of exercises that will lead to weight loss (79).
- Aerobics to get rid of abdominal fat.
- Regular walk for at least 30 minutes.

**Hormonal Replacement Therapy**

Postmenopausal women are at a higher risk of developing metabolic syndromes and CVD. Hormonal replacement therapy (estrogen or estrogen-progestin combined) can be beneficial for them as it would help in maintaining the integrity and function of the endothelium. However, early onset of the therapy in low dosage will be appropriate considering the benefit-to-risk ratio of therapy. Hormone replacement therapy is the treatment of choice for the management of the vasomotor symptoms of depression.
and anxiety in perimenopausal and postmenopausal women (80, 81). Several randomized controlled trials have been conducted to examine the effect of hormone replacement on the components of metabolic syndrome (82). Hormonal therapy has positive effects on weight, abdominal fat, waist-to-hip ratio, and lean body mass. A study on placebo-controlled postmenopausal women showed that combines estrogen-progesterone treatment helped in the prevention of increasing abdominal fat after menopause (83). Another study demonstrated that women of 45-58 years old on 17 beta-estrodiol (E2) of 2 mg and 1 mg norethisterone acetate gained less fat than controls (84). Another study revealed that menopausal hormone therapy users had 25.6% less visceral abdominal tissue, 10.1% lower BMI, 10.4% lower body mass, and 13.2% lower fat mass (85). Therefore, most studies and clinical trials mentioned a decrease in weight, BMI, and fat in patients in hormone replacement therapy; however, some of them reported no change (86, 87). The Nurses’ Health Study involving 21 028 participants was the first prospective study that reported a 20% decreased risk of diabetes by using hormone replacement therapy as compared to those who did not use the therapy (88). Other studies also showed similar results (89, 90). Randomized controlled trials also represented patients on hormonal therapy demonstrated a decrease in insulin resistance as compared to the placebo group without any hormonal replacement therapy (91). The relative risk of developing diabetes and incidence of diabetes also decreased in women who used hormone replacement therapy (92, 93). In some other studies, the hormone replacement therapy also confirmed an increase in HDL and triglycerides while a decrease in LDL in comparison to the placebo group (94-96). The clinical trials depicted that patients on hormone replacement therapy showed improvements in their lipid profiles with a more pronounced effect on oral agents than transdermal ones (97). The impact of hormonal therapy on the blood pressure of an individual varies depending on the cardiovascular condition of an individual before treatment initiation (98-100).

**Lipid-lowering Therapy**

Lipid-lowering therapy should be taken up, along with lifestyle modifications for treating dyslipidemia. The primary target of lipid-lowering therapy is LDL cholesterol and triglyceride. Triglyceride is a secondary target to lipid-lowering therapy for decreasing cardiovascular risks (101). Derivatives of fibric and nicotinic acids can both decrease the levels of triglyceride while increasing HDL cholesterol levels (102). They are often used as a combination therapy with statins under proper precautions. Niacin is inexpensive and can be employed as a monotherapy for treating dyslipidemia in metabolic syndrome but can lead to increased glucose levels. Lipid abnormality-associated metabolic syndrome is related to moderately elevated triglyceride and reduced HDL, but not elevated LDL. LDL levels in the presence of LDL particles which are small and dense may underestimate the cardiovascular risk. Thus, dyslipidemia in metabolic syndrome must be treated in addition to the treatment of elevated LDL cholesterol. LDL particle size should be measured for identifying women with cardiovascular risks and targeting them for lowering their lipid levels.

**Conclusion**

The increase in awareness of the symptoms of postmenopause may help in the early detection of metabolic syndrome that may lead to the symptoms. The management of the disease becomes easier as the metabolic syndromes appearing after menopause can serve as markers for related health treatment. Although postmenopausal symptoms are common for all women, ethnicity, geographical location, current health condition, and social life might affect the incidence and prevalence of these symptoms. Thus, postmenopausal conditions should be taken care of, and women of all groups must have enough knowledge on how to take care of physiological conditions and seek treatment when and if required to lead a normal life.

**Authors’ Contribution**

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**References**

3. Makara-Studzińska MT, Krzy-Noszczyk KM, Jakiel G. Epidemiology of the symptoms of menopause - an
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65. Suárez-Ortegón MF, Ensaldo-Carrasco E, Shi T, McLachlan S, Fernández-Real JM, Wild SH. Ferritin, metabolic syndrome


10.1038/s41598-022-27182-y

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