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Metabolic syndrome in menopause

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Abstract

As women transition to menopause, their risk of cardiovascular disease increases. The risk is mediated by a cluster of abnormalities, the 'metabolic syndrome': dyslipidemia, insulin resistance, hypertension, and obesity. The risk is proportional to the duration of menopause, although ethnic differences were reported. Other contributing factors include estrogen deficiency, inflammatory markers, history of gestational diabetes mellitus, preeclampsia, and polycystic ovary syndrome. Susceptibility to metabolic syndrome is mediated by genetic and lifestyle factors. Intervention to prevent metabolic syndrome must begin early with physical exercise, proper nutrition, and, where indicated, nutritional supplements. Although initial results of the Women's Health Initiative suggested that hormone therapy after menopause led to adverse outcomes, further studies, such as the Early versus Late Intervention Trial with Estradiol (ELITE) study and the Kronos Early Estrogen Prevention Study (KEEPS), showed cardiovascular benefits if hormone replacement is begun early in women not at high risk of cardiovascular disease. A personalized preventive approach must be applied.

Keywords

cardiovascular disease, inflammation, metabolome, MASH, lifestyle, WHI, ELITE, KEEPS

Introduction

Menopause is marked by the natural cessation of menstruation and, thereby, a woman's reproductive years. It is arbitrarily defined as the absence of menstrual periods for 12 consecutive months. Menopause sets in gradually, preceded by a transition period called perimenopause or the menopausal transition [1]. The phases of pre-menopause and postmenopause are defined without universally accepted criteria, which

makes it difficult to compare results from different studies. Ambikairajah et al. [2] reported that the definition of postmenopause was not consistent, often based on varying criteria, like amenorrhea or the final menstrual period, hormone levels, hormone replacement therapy, or even no definition at all. They called for strict diagnostic criteria to establish regular menstruation (e.g., number of menstrual cycles of at least 3 months). The diagnosis may be further refined based on normative age ranges as supplementary criteria in the definition of stages of reproductive aging. Pre-menopause or menopause, however defined, is a period when cardiometabolic dysfunction begins, leading to increased risk of cardiovascular disease (CVD). Risk factors include insomnia and sleep disturbances, obesity, especially abdominal, dyslipidemia, hypertension, diabetes, and psychological disorders, including anxiety and mood disorders. These fall under the umbrella term metabolic syndrome, which encompasses dyslipidemia, insulin resistance, hypertension, and obesity, which increases the risk of CVD.

Metabolic syndrome was long in getting identified and defined, and is still a work in progress. At the turn of the 20th century, it was observed that a combination of hypertension, hyperglycemia, gout, and visceral obesity could lead to diabetes and CVD [3]. In the mid-1940s, upper-body obesity was associated with metabolic abnormalities found in subjects with diabetes and CVD [4]. In rapid succession, Reaven [5] described syndrome X, a cluster of risk factors and insulin resistance, which led to the development of diabetes mellitus and CVD. The syndrome was later called by different terms, including "The Deadly Quartet" [6] and (again) as "The Insulin Resistance Syndrome" [7]. Arriving at a standard definition of metabolic syndrome has many challenges because insulin resistance is the only key factor that is universally agreed upon. There is no consensus on the importance of related conditions such as hyperglycemia, dyslipidemia, hypertension, and central obesity. Different organizations gave differing emphasis to each of these [8]. Insulin resistance and or obesity have been considered the underlying factor in the pathogenesis of the syndrome, but there are alternate definitions not requiring their presence.

The first formal definition of metabolic syndrome came from the World Health Organization (WHO) which proposed insulin resistance (impaired glucose tolerance, impaired fasting glucose, type 2 diabetes or low insulin sensitivity), along with two or more of the following: central obesity [waist hip ratio > 0.9 for men or > 0.85 for women and/or body mass index (BMI) > 30 kg/m^2], triglycerides equal to or above 150 mg/dL and/or high-density lipoprotein (HDL) cholesterol < 35 mg/dL in men or < 39 mg/dL in women, blood pressure equal to or above 140/90 mmHg and microalbuminuria equal to or above 20 ug/mg creatinine [9].

The European Group for the Study of Insulin Resistance (EGIR) proposed a revised version of the WHO criteria: the obesity measure was taken as waist circumference of 94 cm for men and 80 cm for women; the presence of diabetes was an exclusion criterion [8].

The 2001 definition by the National Cholesterol Education Program (NCEP) and Adult Treatment Panel III (ATP III) focused more on cardiovascular risk factors and less on insulin resistance. The criteria were: abdominal obesity, dyslipidemia, hypertension, and insulin resistance or glucose intolerance. Presence of three or more risk factors was considered in the diagnosis: waist circumference equal to or more than 102 cm for men or equal to or more than 88 cm for women, triglycerides equal to above 150 mg/dL, HDL cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, blood pressure equal to or more than 130/85 mmHg and fasting blood glucose equal to or more than 110 mg/dL [8]. The ATP III criteria were modified by the American Association of Clinical Endocrinologists in 2001, and named 'Insulin Resistance Syndrome', bringing insulin resistance back to focus. In this flexible definition, criteria included insulin resistance, elevated triglycerides, reduced HDL cholesterol, and elevated blood pressure [10]. Finally, the International Diabetes Federation (IDF) in 2005 [11] proposed yet another set of criteria that could be used globally both in epidemiological studies and in clinical practice: central obesity was mandatory, with two or more of any other metabolic risk factors of NCEP ATP III. The IDF criteria used ethnic specific cut-off points for waist circumference: equal to or more than 90 cm for men and equal to or more than 80 cm for women of South Asian, Chinese, and Japanese [12]. A Chinese study reported a waist circumference of 85 cm for men and 75 cm for women as risk factors for CVD [13]. Arriving at a definition

of metabolic syndrome is still an ongoing process. Recently, the term metabolic syndrome has been expanded to focus on the Cardiovascular-Renal-Hepatic-Metabolic (CRHM) components [14]. A comprehensive review of the different classifications of Metabolic syndrome by different organizations has been provided by Neeland et al. [15].

In general, menopause is considered the permanent cessation of ovarian function as noted by the absence of menstrual periods for 12 months consecutively [16, 17].

Health issues with menopause

Menopause and perimenopause are associated with a number of conditions, including metabolic syndrome and CVDs, diabetes mellitus, musculoskeletal disorders, cancers, respiratory diseases, depression, dementia, migraine, besides the well-recognized vasomotor symptoms [18].

Women in the Western world most often die of CVD; the mortality is 205.7 per 100,000 for white females, and 286.1 per 100,000 for black females, compared to 294.0 per 100,000 for white males, 405.9 per 100,000 for black males [19]. Women generally have the onset of CVD about 10 years later than men. Premenopausal women are protected from CVD compared to men at a similar age [16]. At the menopause, women tend to develop android obesity with an increase in visceral fat, a precursor of cardiovascular death; simultaneously, there is sarcopenia, generally due to reduced physical activity. The levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and lipoprotein(a) are elevated, while HDL cholesterol is low. Increased CVD risk is mediated by their interaction with other social and behavioural risk factors. These include lower education, greater psychological stress, limited access to health care, barriers in the built environment, poor economic status, poor health literacy, discrimination, and lack of social support [20]. Associated behavioural risk factors are smoking, sedentary lifestyle, improper diet, and poor compliance with treatment. Other factors, such as hormonal imbalance during menopause and pregnancy complications, can lead to a greater risk of myocardial infarction and stroke [21].

Metabolic health and menopause

The menopause marks not only the end of reproduction, but also presages the risk of a number of adverse metabolic health events. Increased risk of CVD is principally caused by ectopic deposition of adipose tissue, leading to chronic inflammation, endothelial dysfunction, and a pro-coagulative state [21]. Loss of protective effects of estrogens by maintaining higher levels of HDL cholesterol and lower LDL cholesterol also contributes. The prevalence of metabolic dysfunction-associated steatohepatitis (MASH), previously called non-alcoholic fatty liver disease (NAFLD), is increased in the postmenopausal phase [22]. Hypertension, which is more common in the postmenopausal age, is a contributor to CVD risk. Inflammatory markers such as IL-2, IL-4, IL-8, IL-10, monocyte chemoattractant protein-1, TNF-α, and other cytokines could contribute to hypertension. Others include alterations in reactive oxygen species, plasminogen activator inhibitor, leptin, adiponectin, and resistin [23].

Gender differences in insulin resistance

Insulin resistance underpins the pathogenesis of metabolic syndrome. Gender differences impact insulin resistance [24]. The essential differences in the metabolism of women compared to men are: increased fat mass deposited chiefly in the subcutaneous tissue, greater insulin sensitivity, non-esterified fatty acid oxidation during exercise, and glycemic excursions following a meal. Particularly, estrogen results in improved insulin sensitivity, a decrease in oxidative stress, enhanced hepatic insulin response, reduced insulin release during fasting, and regulates insulin release after meals. In addition, it improves insulin-stimulated glucose absorption in the skeletal muscle and promotes vasodilatation by enhancing nitric oxide production [24].

Progress of metabolic syndrome across the menopause

Apart from the physiological and biochemical alterations observed after menopause, earlier events also influence the occurrence of metabolic syndrome: increased parity contributes to the risk, via insidious weight gain, while lactation is protective. Other risk factors include gestational diabetes mellitus, preeclampsia, and polycystic ovary syndrome [25]. Aging is associated with metabolic abnormalities, including an increase in obesity, CVD, type 2 diabetes, hypertension, and non-inflammatory diseases, such as stroke. However, Kim et al. [26] reported that among Korean women, the risk of metabolic syndrome was independent of the normal aging process, although there is a biological basis for a combined predisposition. A systematic review and meta-analysis from Iran showed that nearly 50% of postmenopausal women had metabolic syndrome [27].

Gurka et al. [28] studied the relationship between the severity of metabolic syndrome and the stage of menopause in a United States cohort (n = 1,470) drawn from the Atherosclerosis Risk in Communities. The background for this study was to assess the time of onset and progression of metabolic syndrome: premenopausal or postmenopausal in two ethnic groups. Women of colour showed higher waist circumference at baseline, systolic blood pressure, and glucose, but had lower triglycerides and were more likely to have hypertension. White participants were more likely to be taking hormonal replacement therapy. The rate of increase in MetS severity during the premenopausal period was more rapid among black than among white women [28]. Even when adjusted for socioeconomic and hormone use, black women had a slower progression of MetS Z-scores during the postmenopausal period relative to earlier periods. In addition, participants taking estrogen replacement therapy after menopause was high, being higher among white than black women. This underscores the need to have ethnic specific criteria for the diagnosis of metabolic syndrome. In addition, considering the different risk trajectories and interventions between the ethnic groups, focus must be made on identifying and lowering triglyceride levels, and offering hormone therapy for black women [19]. Another possibility for the difference was ascribed to changes in the rate of reduction of estrogen effects on adipocytes and the liver. Metabolomic analysis in menopause revealed a significant increase in ApoB along with VLDL cholesterol particles [29]. Further studies must be carried out to understand the mechanisms of these ethnic differences.

Analysis of the differences in food portion imbalances showed that those with metabolic syndrome generally ingested more refined starchy bakery products, sugary cereals, sweet biscuits, cakes, and sweets [30].

Comparison among gene signatures of metabolic syndrome, type 2 diabetes, cardiovascular disease, and menopausal status

Common gene signatures and the accompanying signalling pathways of metabolic syndrome, type 2 diabetes mellitus, CVD, and menopause status revealed interesting observations. The purpose of the study was to identify genetic and epigenetic signatures responsible for shared molecular mechanisms [31], which could be used as potential biomarkers. DisGeNET knowledge management platform was used to integrate gene-disease associations from several public sources. MalaCards, another platform that integrates all disease lists to list out related genes, pathways, and gene ontologies associated with the disease of interest. Microarray data, used to monitor the simultaneous expression of thousands of genes, were obtained from nine premenopausal and ten postmenopausal healthy women. Mechanistic insights into the selected genes were obtained from gene set enrichment and pathway analysis by platforms such as Kyoto Encyclopedia of Genes and Genomes (KEGG), ClueGO. ClueGO and CluePedia were used together to search for new markers potentially related to pathways [31]. Further, the protein-protein interactions (PPIs) network identified key genes and gene modules involved in menopause.

The prevalence of metabolic syndrome is higher in postmenopausal women compared to those who were premenopausal. Postmenopausal women had abdominal obesity, hypertension, and high fasting plasma glucose as the most frequent components; premenopausal women had decreased HDL cholesterol in place of hypertension. In order to find the gene signature associated with the three conditions postmenopause, DisGeNET and Malacards databases were mined for a list of disease genes. The genes

associated with metabolic syndrome (n = 1,125), CVD (n = 1,756), and type 2 diabetes (n = 31,134) overlapped. These were similar to earlier studies.

It is clear that gene association studies with diseases are useful if they provide information about the cause and progression of the disease. Results of Gene Ontology (GO) pathways showed that shared genes were enriched in elevated blood pressure; they were also consistent with the concept that lipid abnormalities are responsible for the development of metabolic syndrome, type 2 diabetes, and CVD. The KEGG pathway analysis suggested that genes that were enriched belonged to signalling pathways of p53, prolactin, parathyroid hormone, and calcium homeostasis. Since polygenic diseases result from a complex interaction among genes, PPI network of shared genes was constructed in the STRING database and visualized by Cytoscape. The most significant shared genes occurred with ESR1, EGFR, MMP2, MMP9, TNF, and IL-6. A summary of all these genes and gene modules points to the relationship between inflammation (chronic and systemic) and increased risk of CVDs [31].

Metabolic syndrome in relation to the duration of the postmenopausal period

Cho et al. [32] studied 1,002 women (618 premenopausal and 384 postmenopausal) to assess the influence of postmenopausal status on the prevalence of the metabolic syndrome according to years since menopause. Expectedly, postmenopausal women had a higher mean age, weight, BMI, waist circumference, blood pressure, HOMA-IR, total cholesterol levels, LDL cholesterol, and triglycerides; but HDL cholesterol was lower. There was no significant difference in the fasting plasma insulin levels. The prevalence of metabolic syndrome peaked between the ages of 60 and 69 and declined thereafter. The authors provided a range, but no data on the actual peak prevalence. For a multivariate logistic regression analysis adjusted for age and BMI, the risk for metabolic syndrome in postmenopausal women increased with years since menopause, reaching peak levels in the 10- to 14-year group. This was independent of age and BMI [32].

A more recent study from Turkey assessed the effect of duration of menopause on the risk factors of the metabolic syndrome [33]. Seven hundred and five women between the ages of 45 and 60 were cross-sectionally assessed; they were divided into two groups based on the duration of the postmenopausal period: 438 had been menopausal for one to five years, and 267 for six to ten years. Women who had a longer postmenopausal phase had a higher risk of metabolic syndrome [33], showing that metabolic health in the postmenopausal phase of life must be monitored. The authors did not present data on the risk of metabolic syndrome and the duration of perimenopause. This would be a productive area for future research. From the available information, the presence of metabolic syndrome components, ethnicity, and the use of hormone therapy could account for differences in the duration of pre-menopause and prevalence of metabolic syndrome.

Metabolic dysfunction-associated steatohepatitis, previously called non-alcoholic fatty liver disease and metabolic syndrome

MASH/NAFLD is a metabolic condition that is closely linked to insulin resistance and metabolic syndrome, with a bidirectional association [23]. It is more common in men than in premenopausal women due to the protective effect of estrogens in women; a similar risk is observed with gestational diabetes and polycystic ovary syndrome. MASH is a multisystem disease that can lead to coronary heart disease, independent of age. However, discrepancies in gender were reported, due perhaps to differences in populations studied and diagnostic measures employed [23]. From an extensive analysis of 180 studies, 19 met the inclusion criteria to assess the influence of menopause, insulin resistance, and BMI on the prevalence of NAFLD [34]. The majority of the studies (n = 17) showed an increased prevalence in postmenopausal women, while only two did not.

NAFLD is characterized by the deposition of fat in the liver in the absence of alcohol consumption, rare genetic disorders, or hepatotoxic drugs; it results from an imbalance between the deposition (increased uptake of fatty acids) and the (decreased) disposal of lipids in the liver.

Post menopause, the levels of ovarian hormones are reduced; animal studies have shown a correlation between menopause and hepatic deposition of fat, which may account for NAFLD. Kamada et al. [35] assessed the effects of estrogen on NASH in ovariectomized (OVX) mice, which were fed a high-fat and high-cholesterol (HFHC) diet. In order to study the effects of estrogen deficiency, OVX mice and sham-operated (SO) mice were fed normal chow or HFHC diet for six weeks; later, the effects of exogenous estrogen replenishment were studied on OVX mice fed with an HFHC diet treated with implanted hormone release pellets (containing 17β-estradiol or placebo vehicle) for six weeks. Estrogen deficiency accelerated NASH progression in OVX mice that were fed an HFHC diet; this effect was improved by estrogen therapy. They further reported that HMG-CoA reductase inhibitors pitavastatin and rosuvastatin attenuated the accelerated progression of steatohepatitis in OVX mice fed an HFHC diet [36, 37]. Regulation of lipid and glucose metabolism in the adipose tissue and liver is dependent on 17β-estradiol. In addition, there is an imbalance of androgens and reduced sex hormone-binding proteins, leading to abdominal fat deposition, which worsens with age. The liver is unable to oxidize fatty acids efficiently in the menopause, leading to ectopic deposition in the liver and abdominal viscera. Use of hormone replacement therapy (estrogen and or progesterone) may further affect the hormonal milieu and result in NAFLD. Thus, sex-specific prediction models could help in personalizing management approaches for women [34].

Other pathogenic factors leading to metabolic syndrome in the menopause

Gut microbiota

Up to 1,000 bacterial species, numbering about 100 trillion, inhabit the human colon. They encode around 3 million genes, which may impact the development of metabolic syndrome and other disorders [38]. Their collective genome, or the microbiome, may be considered a separate organ and is influenced by many factors, including gender and sex hormones after puberty.

Estrogens produced in the body or ingested in food can be metabolized by gut microbes and thereby influence the host. Some of the bacteria exhibit beta-glucuronidase activity, which deconjugates conjugated circulating estrogens excreted in the bile. Gender difference was shown to influence the development of metabolic diseases [39]. The influence of sex hormones on gut microbiota has been termed microgenderome; this term refers to sex differences in the gut microbiome and their interactions with hormones and the immune system.

Sleep

Most natural biological processes, including hormone release and blood glucose levels, have diurnal cyclical patterns [40]. Interference with this cycle promotes obesity and affects insulin sensitivity and lipid metabolism. Improper and insufficient sleep is an important modifiable risk factor for obesity, insulin resistance, and type 2 diabetes mellitus [41, 42]. Sleep disorders show a gender difference, resulting from the unique biology in women [43]. Women with disordered sleep breathing are often diagnosed late because of less snoring, more rapid eye movement (REM) apnea, and less non-REM (NREM) apnea; in addition, they have shorter airways, smaller lungs, smaller diaphragm, greater peripheral distribution of fat, and lower chemosensitivity. Restless legs syndrome, which is more distressing, is twice as common in men. It is associated with depressive symptoms and is a potential cardiovascular risk factor [43]. Deficiency of iron and of vitamin D is often found in women with restless legs syndrome. Brain tissue, which is sexually dimorphic, is influenced by sex hormones.

Premature ovarian failure (POF) or primary ovarian failure

Primary ovarian failure is the condition where there is insufficient ovarian follicle function before the age of 40 years. It has a global estimated pooled prevalence rate of 3.7% [44] and could be even higher in medium or low-human-development-index nations. It can present in various ways, from primary amenorrhea due to ovarian dysgenesis or with a secondary amenorrhea due to different congenital or acquired abnormalities. It not only affects fertility but also has adverse long-term effects on bone, cardiovascular, and cognitive health. Often, the underlying causes remain unknown. Recently, a number of genetic causes and syndromes

have been identified [45]. Other recognized causes include autoimmune and iatrogenic (following surgery, chemotherapy, or radiotherapy). Toxic, metabolic, or infectious causes are uncommon. They can present with menstrual irregularities or secondary amenorrhea, associated with hypoestrogenic symptoms. The symptoms are usually more pronounced than those typical of climacteric, especially in acquired forms with sudden onset. Natural and surgical menopause are associated with a higher incidence of CVD [46]. All women with POF are advised to take hormone replacement until the average age of menopause. The outcome of hormone therapy would be known from the Premature Ovarian Insufficiency Study of Effectiveness (POISE) of hormonal therapy UK randomized trial [47].

Circulating metabolome in menopause

Karppinen et al. [48] assessed changes in the circulating metabolome, or the complete set of small-molecule chemicals found in the circulation, in relation to menopausal hormonal shift among women who were either transitioning to menopause or were in early menopause. Compared to clinical and conventional biochemical measures, metabolomics offers a broader picture of menopausal changes. In order to identify if menopause is associated with an identifiable metabolic fingerprint, a random sample of 218 Finnish women was taken from the Estrogenic Regulation of Muscle Apoptosis (ERMA) prospective study. Baseline mean age of participants was 51.9 years (SD: 1.9 years); they were followed up for a median duration of 14 months (range: 4 months to 3.5 years). Menopause was associated with significant changes in 85 metabolic measures [48]. During menopausal transition, there was a pro-atherogenic change in the metabolome. Particularly, the hormonal shift associated with menopause was responsible for alterations in lipoproteins. Menopausal hormone therapy corrected the change through metabolism of LDL cholesterol, HDL cholesterol, and glycine. This provided evidence that during menopause, the circulating metabolome is influenced by changes in female sex hormones [48]. Therefore, measurement of the metabolome in the peri-menopausal stage has the potential to identify proatherogenic changes, providing scope for early preventive therapy [48]. Signals from the metabolome can help in personalizing lifestyle measures and hormone therapy in those women carrying at-risk metabolites.

Other factors

Hyvärinen et al. [49] studied whether indicators of metabolic health change around the menopause and found any relationship to physical activity. Two hundred and ninety-eight women aged 48–55 years at enrolment in the ERMA and EsmiRs studies were followed up for 3.8 years (SD: 0.1 years). Physical activity was measured with triaxial ActiGraph GR3X and wGT3X accelerometers [49]. It was confirmed that menopause may accelerate the changes in multiple indicators of metabolic health. Physical activity led to a healthier blood lipid profile and body composition. The authors did not present data on the quantum of physical activity that improved the metabolic profile. According to the WHO guidelines of 2020 on physical activity, adults and older adults with chronic conditions are recommended to perform at least 150–300 min of moderate-intensity aerobic physical activity, or at least 75–150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for substantial health benefits [50].

Individuals from certain endogamous ethnic pockets harbour variants of the hepatic enzyme butyrylcholinesterase. A well-established phenotypic expression of this variant is the development of prolonged apnea following the administration of the muscle relaxant succinylcholine. The association of variant enzymes with roles other than pharmacogenetics was studied. It was shown to influence the development of insulin resistance and of cognitive decline [51, 52]. An animal study showed that butyrylcholinesterase activity was decreased in the serum of rats that were OVX and might therefore contribute to the impaired cognition associated with the menopause [53]. It is therefore possible that variant forms of butyrylcholinesterase could influence the onset and course of metabolic syndrome in the menopause. In contrast to the findings in OVX rats, a clinical study of butyrylcholinesterase levels in pre- and postmenopausal women showed that postmenopausal women had elevated levels of the enzyme (13,809; SEM: 3,266 U/L vs. 7,582; SEM: 1,532 U/L) [54]. Elevated levels of butyrylcholinesterase could be

due to disinhibition of its production from the liver, which may be associated with increased circulating lipid levels. Subjects with diabetes mellitus showed an inverse association of LDL cholesterol and serum butyrylcholinesterase [55].

Prevention and management of metabolic syndrome in menopause

Treatment of metabolic syndrome in menopause must begin with prevention well before menopause. Similar principles of prevention are applicable to all components of metabolic syndrome [56]. The following discussion focuses on those characteristics that are relevant to prevention and treatment in menopause.

Physical activity and exercise training

Lifestyle interventions form the foundation for preventing metabolic syndrome. Physical activity is beneficial in attenuating the adverse effects associated with metabolic syndrome during menopause. Tan et al. [57] published a systematic review and meta-analysis of randomized controlled trials on the effects and efficacy of exercise on the various components of metabolic syndrome risk among postmenopausal women. Eligible studies comprised 2,132 participants. Overall, exercise training improved all metabolic syndrome risk factors. In sub-group analysis, moderate intensity and combined exercise training improved all risk factors except for HDL cholesterol. Combined exercise was more effective. Long duration of training (≥ 12 weeks) improved risk factors except for triglyceride levels [57]. Further studies are required to apply these findings to wider and elderly populations.

Nutrition

Nutrition plays a key role in preventing metabolic syndrome. A recent review on the importance of nutrition in perimenopause and menopause concluded that modifiable factors include rapidly acting sugars, smoking, alcoholic drinks, sedentary lifestyle, excess salt, and restriction of saturated fats to below 10% of total daily energy intake [58].

A protein intake of 0.8–1.2 g/kg/day is desirable, of which half is preferably from plant sources. Other required dietary components are calcium, vitamin C, B complex vitamins, vitamin D, n-3 LCPUFA, and omega-3 fatty acids. Vegetables and fruit in five portions (300–400 g of vegetables and 100–200 g of fruits) and legumes are best consumed at least once a week. It is advisable to consume less than 500–700 g of boiled, steamed, or fried per week, along with at least one meat-free day a week. Protein sources can be obtained from eggs, fish, dairy, and a combination of legumes, nuts, and grains.

Sunflower oil is advisable for frying, and olive, rapeseed, or soybean oil for salad dressings. Deep-sea fish with fatty meat (salmon, mackerel, tuna, and sardines) or freshwater fish (trout, silver carp) can be consumed at least twice a week (100–120 g on each occasion). Unsalted nuts (30 g/day) are healthy, while helping to maintain body weight. Fibre-rich food is recommended: 30–45 g/day, preferably as whole grains.

Nuts

Nuts form an integral part of the Mediterranean diet, which has been shown to lessen metabolic syndrome. They have a high proportion of unsaturated fat, fiber, and bioactive compounds. Nuts have a beneficial effect on lipid and carbohydrate metabolism [59], both of which are disturbed in metabolic syndrome.

Isoflavones in soybeans

The known biological actions and consequent health benefits of soy products are attributed to their isoflavone content. While a popular treatment for menopause-related symptoms, its precise role is still open to question. Many factors, such as processing (cleaning, drying, crushing, dehulling), extraction to produce refined oil, and the remaining components (inorganic minerals and small molecules) [60], may modify beneficial effects. However, it is reported that a higher intake of isoflavones is associated with a moderately low risk of developing coronary heart disease.

Fish intake

Fish are a good source of nutrients, having metabolic importance as they have omega-3 fatty acids, selenium, iodine, vitamin D, taurine, and carnitine. They are a good source of high-quality protein with a low-calorie content. A number of interventional and observational studies demonstrated that regular fish consumption had a positive impact on maintaining body weight, blood pressure, and glucose homeostasis, thereby lowering the risk of metabolic syndrome [61]. Protection was most pronounced in individuals who consumed lean, unfried fish.

Protection may be due to increasing satiety via the release of tryptophan, a longer period of digestion, and lowering of insulin resistance through anti-inflammatory actions of their omega-3 fatty acids [61].

Spirulina supplements

Spirulina is a filamentous cyanobacterium with photosynthetic capability, which grows in the salted alkaline lakes found in Africa, Asia, Mexico, and America. It has immunomodulatory and antihypertensive effects. Spirulina has been used as a supplement to prevent all elements of metabolic syndrome [62]. In a review of 20 studies, Bobescu et al. [62] showed that spirulina had positive effects in the management of different components of metabolic syndrome. However, further work is needed to determine the optimal dose and duration of intake.

Nutraceuticals and functional foods

Nutraceuticals and functional foods can help prevent metabolic syndrome and cardiovascular events by their effects on maintaining cellular redox balance, preserving endothelial integrity, and reducing inflammation. There are few clinical studies that assessed their effect in postmenopausal women to prevent CVD [63]. In an animal model, the antioxidative and anti-inflammatory properties of extracts [*Cnidium officinale*, *Pueraria lobata* Ohwi, and *Leonurus japonicus* (CPL)] were assessed on vascular endothelial dysfunction [64]. The extracts were protective against vascular endothelium dysfunction in OVX rats by reducing inflammation and upregulating vasodilation. Similar effects were observed with danshen aqueous extract [65]. Further work is necessary to determine the ideal dose, duration, and potential side effects of the supplements.

Critique: role of dietary supplements

As is evident from the diverse interventions in both animal models and humans, supplements can play a supporting role by improving overall metabolic health. Further translational studies are needed to determine the indication, result, and dose at which they are given. At present, they have a supplementary role, without definite evidence of their efficacy, although a theoretical basis exists that they may be useful. The reason for interest in dietary supplements and natural products is because of the low cost and potential adverse effects of traditional pharmaceuticals. Therefore, the role of natural products, including herbs, botanicals, vitamins, minerals, probiotics, and dietary supplements in metabolic syndrome is being explored. A recent scoping review concluded that it is 'advisable to conduct further extensive research to assess the efficacy of these products, potentially integrating them into treatment regimens for individuals with metabolic syndrome' [66].

Precision nutrition

Clinical studies have shown the benefits of different diets in the prevention of CVD; the two prominent ones are the Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean (MED) diet [56]. To truly understand the effects of these interventions in specific groups, such as postmenopausal women, deep genotyping studies using single-nucleotide polymorphisms (SNPs) are more useful to predict differential responses to low-fat and low-carbohydrate diets at an individual level. Personalized diet prescriptions can be given depending on the genotypes, family history, medication use, microbiome diversity, and proteome [56]. Advanced statistical techniques and deep learning can contribute to a synthesis of the diverse data and distil information that is relevant to the individual subject.

Hormone replacement therapy and metabolic syndrome

Considering the adverse health effects of estrogen deficiency at the menopause, the Women's Health Initiative (WHI) was a large randomized placebo-controlled trial to assess the effects of hormone replacement therapy for the prevention of chronic disease among healthy postmenopausal women (mean age: 63 years). The results showed a paradoxical increase in the incidence of cardiovascular events in older women given conjugated equine estrogens (CEE), in contrast to the beneficial effects observed in symptomatic menopausal women given estrogens earlier in the menopause. The results were re-analyzed, taking into account the type of drug used as well as the duration of menopause when the intervention was begun (mean age of 63). They were carried out because of the contradictions between observational studies and the WHI [67]. Earlier, a number of observational studies on hormone therapy showed a lowered incidence of CVD in women with symptoms observed during early menopause [68]. The ability of estrogen to increase HDL and decrease LDL suggests that hormone replacement therapy can be given as a prophylaxis against coronary artery disease. These were supported by observational studies, which suggested that women taking estrogen had a lower risk of coronary artery disease than women not taking estrogen [69]. However, the results of the WHI showed an increase in cardiovascular events in older women who were given CEE. In order to reconcile the divergent reports among the observational studies and WHI, further sub-analyses were carried out.

Women's Health Initiative

The WHI was designed as a large and complex clinical investigation of strategies to prevent and control common causes of morbidity and mortality in postmenopausal women. It was initiated in 1992, with a planned completion date of 2007. Postmenopausal women (ages 50 to 79 years) at WHI clinical centers (n = 40) were recruited into either a clinical trial (n = 64,500) or an observational study (n = 1,000). One of the arms was of hormone replacement therapy, hypothesized to reduce the risk of coronary heart disease. Women who were ineligible or unwilling to enroll were invited to enroll in the observational study [70].

In all, 16,608 postmenopausal women aged 50–79 years with an intact uterus at baseline were recruited between 1993 and 1998. They received CEE, 0.625 mg/day, plus medroxyprogesterone acetate (MPA), 2.5 mg/day, in 1 tablet (n = 8,506) or placebo (n = 8,102). The primary outcome measure was coronary heart disease (nonfatal myocardial infarction and coronary heart disease death). After a follow-up of a mean of 5.2 years, the trial of estrogen plus progestin vs. placebo was stopped because the global index statistic showed that risks exceeded benefits. Absolute excess risks per 10,000 person-years attributable to estrogen, along with progestin, were seven more CHD events [71].

When health outcomes of the WHI trials were assessed during the intervention and extended phases after stopping estrogens, hormone therapy had come up with a complex pattern of risks and benefits. The authors concluded that the results do not support the use of this therapy to prevent chronic diseases [72]. Use of CEE with MPA for 5.6 years (median) or with CEE alone for 7.2 years (median) was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years [73].

Early versus Late Intervention Trial with Estradiol (ELITE) and Kronos Early Estrogen Prevention Study (KEEPS)

ELITE and KEEPS studies assessed whether the timing of hormone replacement had an effect on the prevention of CVD.

ELITE was designed to specifically test whether the timing of postmenopausal hormone therapy could account for the results of WHI. In the randomized, double-blind, placebo-controlled trial, 643 healthy postmenopausal women who did not have CVD were randomized to receive oral estradiol or placebo for up to 6 to 7 years [74]. Using arterial wall ultrasound echomorphology as a measure of arterial wall morphology, oral estradiol reduced atherogenic progression of arterial wall composition in healthy postmenopausal women within six years of menopause [75].

The KEEPS was a randomized, double-blind, placebo-controlled trial to study the effects of menopausal hormone treatments on the progression of carotid intima-medial thickness in women who recently reached menopause (< 3 years of menopause). They did not have a history of CVD and were given either oral CEE (0.45 mg/day) or transdermal 17β-estradiol (50 μg/day), both with progesterone (200 mg/day for 12 days/month), or placebo pills and patches for a period of four years [76]. At the end of four years, hormone therapy did not alter the rate of increase in carotid artery intima-media thickness. There was, however, a trend for reduced accumulation of coronary artery calcium with the use of oral CEE. There were no serious adverse effects [77].

In summary, hormone therapy that includes oestrogen at menopause can reduce adverse cardiometabolic outcomes. It is important to emphasize that comprehensive care must be advocated with attention to nutrition and physical activity, reduction or avoidance of alcohol consumption and smoking, along with management of other risk factors [78]. One should bear in mind that in women aged less than 60, stopping hormone therapy led to increased risks of cardiac-related death [79]. Hormone therapy in women with metabolic syndrome requires close attention to lifestyle changes (Table 1) followed by a careful selection of estrogenic and progestational agents; attention must be paid to individualize doses, routes, and duration of administration. Menopausal hormone therapy differs from therapeutic doses (Table 2). Starting treatment is timed early in perimenopause, and patient selection occurs after identifying risks to cardiovascular, metabolic, cancer history, and history of undiagnosed genital tract bleed. Especially, women at very high cardiovascular risk must avoid menopausal hormone treatment [80]. In addition, unscheduled bleeding with hormone therapy must be carefully worked up. The patient should understand the advantages of lifestyle behavior and that hormone therapy is only an additional measure.

Table 1. Lifestyle Interventions to minimize or prevent metabolic syndrome in menopause.

Lifestyle	Intervention	Comment
Sleep	Duration	7–8 hours/night
	Bedtime	Between 10 and 11 pm
	Screen view	To avoid TV and phone 2 hours before bedtime
Nutrition	Balanced, optimal*	To maintain a BMI < 25
	Meal timings	To eat meals within a 14-hour time window
Smoking, alcohol	To avoid or stop	
Physical activity	Essential	Combine CV fitness, weights, flexibility, and balance
		Aim to take 8,000–10,000 steps a day
		If sedentary: move around 5 min hourly

*: Include the following: olive oil, nuts, isoflavones in soyabeans, fish, spirulina supplements, functional foods and nutraceuticals, and calcium. BMI: body mass index.

Table 2. Hormone replacement to minimize or prevent metabolic syndrome in menopause.

Condition	Advice	Comments
Premature ovarian failure or oophorectomy in premenopausal women	Hormone replacement until the expected age of menopause	
With an intact uterus and ovaries	Individualize treatment*	Estradiol valerate patch (1 or 2 mg)
		Micronized progesterone
		Dydrogesterone
		Medicated IUCD

*: Hormone therapy is in addition to lifestyle and behavior interventions to prevent and treat concomitant hypertension, insulin resistance, type 2 diabetes mellitus, dyslipidemia, and obesity: preferably to start early in the perimenopause; rule out contraindications (see main text); must be individualized. IUCD: intrauterine contraceptive device.

Conclusions

It is evident that the time period preceding and following the menopause is associated with metabolic syndrome; the components (insulin resistance, obesity, hypertension, dyslipidemia) increase the risk of CVD. With the available evidence, it is necessary to integrate interventions to prevent or postpone their development. Lifestyle modifications, personalized nutrition, hormonal therapy, dietary supplements, and nutraceuticals to prevent metabolic syndrome with menopause are advocated starting early in life. Attention must be paid to individual factors, including age, and specific metabolic risk profile (Table 1). Further studies are required to determine the outcomes of specific preventive measures other than lifestyle. These include the nature, dose, and timing of hormone therapy as well as evidence for the translation of nutritional supplements into clinical outcomes. It may be anticipated that genetic, metabolomic, and other biomarkers may identify women at higher risk early, which helps guide the start of treatment. One must also dissect age-related changes from those of menopause.

Abbreviations

ATP III: Adult Treatment Panel III

BMI: body mass index

CEE: conjugated equine estrogens

CVD: cardiovascular disease

ELITE: Early versus Late Intervention Trial with Estradiol

ERMA: Estrogenic Regulation of Muscle Apoptosis

HDL: high-density lipoprotein

HFHC: high-fat and high-cholesterol

IDF: International Diabetes Federation

KEEPS: Kronos Early Estrogen Prevention Study

KEGG: Kyoto Encyclopedia of Genes and Genomes

LDL: low-density lipoprotein

MASH: metabolic dysfunction-associated steatohepatitis

MPA: medroxyprogesterone acetate

NAFLD: non-alcoholic fatty liver disease

NCEP: National Cholesterol Education Program

OVX: ovariectomized

POF: premature ovarian failure

PPIs: protein-protein interactions

REM: rapid eye movement

WHI: Women's Health Initiative

WHO: World Health Organization

Declarations

Author contributions

NG, LG, and SRG: Conceptualization, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

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