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Menopause and Exercise: Linking Pathophysiology to Effects

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Abbreviations: BMD: Bone Mineral Density, CVD: Cardiovascular Disease, DHEA: Dehydroepiandrosterone, EPC: Endothelial Progenitor Cell, FSH: Follicle Stimulating Hormone, NO: Nitric Oxide, VSMC: Vascular Smooth Muscle Cell, GnRH: Gonadotropin-Releasing Hormone, HDL-C: High Density Lipoprotein–Cholesterol, ICAM-1: Intercellular Adhesion Molecule 1, LDL-C: Low Density Lipoprotein–Cholesterol, VCAM-1: Vascular Cell Adhesion Molecule 1, SHBG: Sex Hormone-Binding Globulin, LH: Luteinizing Hormone, *IL-6:* Interleukin 6, IL-1: Inteleukin-1, TNF: Tumour Necrosis Factor, RANKL/OPG: Receptor Activator Of Nuclear Factor Kappa B Ligand/ Osteoprotegerin, PTH: Parathyroid Hormone, RCT: Randomized Controlled Trials, ROS: Reactive Oxygen Species, IGF-I: Insulin-Like Growth Factor 1, VMS: Vasomotor Symptoms, WBV: Whole Body Vibration

Introduction

Women spend more than one third of their lives in the postmenopausal state owing to increased longevity, necessitating a clearer understanding of the impact of menopause on body systems, a critical aspect in targeting effective preventive measures. The change in the sex hormone profile, especially the decline in estrogen accompanying menopausal transition plays a key role in the pathogenesis of physical and metabolic derangements in postmenopausal women. Benefits of physical activity and exercise training in preventing and attenuating health risks in the ageing population have long been established but their beneficial effects on the subpopulation of postmenopausal women need further exploration.

The pathophysiology of four key health problems associated with menopause, namely, changes in body composition, cardiovascular disease (CVD), vasomotor symptoms (VMS) and osteoporosis, and how physical activity and exercise training affect them are reviewed here.

Pathophysiology (Table 1)

Changes in body composition

Weight gain in women during and after menopause is a well-recognized phenomenon, which is accompanied by a multitude of changes in body composition. Longitudinal comparisons of similar-aged postmenopausal and premenopausal women showed an accelerated increase in central adiposity in postmenopausal women, caused by a peripheral or subcutaneous to visceral fat redistribution, increase in total adiposity, changes in lipid metabolism and a concomitant decline in lean body tissue [1]. Visceral fat deposition favours the development of insulin resistance and type 2 diabetes mellitus, hypertension, and a proatherogenic lipid profile, leading to increased CVD risk and other effects of overweight and obesity in women after menopause [2]. Muscle loss is primarily due to an imbalance between muscle protein synthesis and breakdown contributed to by an increase in oxidative stress, inflammation and hormonal changes [3].

Alterations in sex hormones play a role in the change in body composition at menopause though mechanisms are unclear. Low estrogen concentrations are thought to influence adipose tissue fatty acid storage and oxidation that may contribute to increases in body fat in postmenopausal women [4], leading to a low-grade inflammatory state with increased pro-inflammatory cytokines contributing to sarcopenia [3]. Decline in estrogen levels has also been linked to increased cortisol, which promotes accumulation of abdominal fat [5]. The androgens; testosterone, dehydroepiandrosterone (DHEA) and androstenedione are also believed to affect muscle mass [6]. The testosterone/ estrogen ratio may even have a greater effect on maintenance of lean body mass than the independent effects of either hormone [7].

Other factors such as chronological aging, quantity, intensity and type of physical activity also contribute to the changes in body

Table 1 Summary of pathophysiological mechanisms for menopause-related health problems.

Problem	Pathophysiology
Changes in body composition	• **Weight gain and increase in total adiposity** by low estrogen influencing adipose tissue fatty acid storage and oxidation, ageing, physical inactivity, poor diet • **Fat redistribution causing central adiposity** by low estrogen increasing cortisol, reduced lipoprotein lipase promotes visceral adiposity and may alter plasma lipid concentrations • **Decreased lean body mass and muscle loss** by decreased muscle protein synthesis and increased breakdown, low estrogen causing low grade inflammatory state with increased pro-inflammatory cytokines and increase in oxidative stress, reduced androgens and testosterone/ estrogen ratio, dietary protein and micronutrient inadequacy
Cardiovascular disease	• **Detrimental effects on the vessel walls** by low estrogen causing decreased EPC and EPC activity diminishing re-endothelialization following arterial injury, low NO bioavailability, increased VSMC proliferation and inflammatory expression of ICAM-1 and VCAM-1 • Contributed to by abnormal lipid profile, high testosterone and low SHBG levels
Vasomotor symptoms	• **Increased vascular reactivity** caused by decreased sympathetic vasoconstrictor activity, increased sympathetic vasodilator activity or other potential mechanisms • **Narrowed thermoneutral zone of hypothalamic thermoregulatory centre** caused by decreased serotonin, increased norepinephrine • Low estrogen is the underlying cause but possibly contributed to by LH fluctuations and reduction in hypothalamic and peripheral β-endorphin
Osteoporosis	• **Estrogen deficiency promoting bone resorption** by possibly increased secretion of osteoclastogenic cytokines (eg. IL-6), imbalance of RANKL/OPG gene expression and inhibition of osteoclast apoptosis possibly contributed to by decreased progesterone, androstenedione, androstenedione/SHBG ratio, inhibin A and inhibin B • **Aging-related** increased ROS and sclerostin inhibit osteoblast proliferation and activity via antagonizing Wnt-β catenine signaling pathway contributed to by increased PTH, decreased IGF-I and decline in physical activity. Decreased mechanical loading diminishes the deformation of bones and fluid shear forces on the skeleton, decreasing bone remodeling

EPC, endothelial progenitor cell; NO, nitric oxide; VSMC, vascular smooth muscle cell; ICAM-1, Intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; IL-6, interleukin 6; RANKL/OPG, receptor activator of nuclear factor kappa B ligand/ osteoprotegerin; PTH, parathyroid hormone; IGF-I, insulin-like growth factor 1.

composition at menopause [8,9]. Dietary practices, specifically protein and micronutrient inadequacy can negatively influence body composition, especially muscle mass [10]. Decreased estrogen, as well as physical inactivity and aging enhance adipose tissue fatty acid storage and oxidation, contributing to the increased body fat and loss body muscle mass in postmenopausal women [8]. The decline in lipoprotein lipase promotes visceral adiposity and may alter plasma lipid concentrations [11].

Cardiovascular disease

The estrogen-replete hormonal milieu of premenopausal females is cardioprotective whereas the male androgenic hormonal profile contributes to the causation of CVD [12]. Experimental and clinical evidence suggest strong associations of declining levels of estrogen with the escalated risk of CVD in older women, particularly during the menopausal transition. In premenopausal women, estrogen is thought to confer its cardiovascular protective effects mainly by facilitating a favorable lipoprotein and lipid profile and by direct effects on the vascular wall. Estrogen promotes endothelial cell proliferation and increased vascular incorporation of bone-marrow-derived endothelial progenitor cells (EPC), enhancing re-endothelialization following arterial injury [13,14]. Estrogen increases nitric oxide (NO) bioavailability [15,16] reduces vascular smooth muscle cell (VSMC) proliferation following vascular injury [16], and inhibits inflammatory expression of the adhesion molecules in endothelium, i.e., vascular cell adhesion molecule-1(VCAM-1) and intercellular adhesion molecule-1(ICAM-1) [15]. Studies on effects of progestins on vascular elements give conflicting results. Data on testosterone and sex hormone-binding globulin (SHBG) suggest that increased androgenicity, characterized by high testosterone and low SHBG levels are associated with an increased CVD risk in postmenopausal women [17]. However, evidence for an association of androgenicity with documented cardiovascular events is lacking [18].

Vasomotor symptoms

Vasomotor symptoms or hot flushes, experienced by up to 80% of women around menopause [19,20], are associated with increased vascular reactivity, where vasodilatation is followed by vasoconstriction [21]. Pathophysiology of VMS is still unclear. Decreased estrogen activity appears to play a prominent role in its etiology, endorsed by estrogen replacement being the most effective treatment for VMS [22,23]. Changes in the neuroendocrine processes in the hypothalamic thermoregulatory centre [24-26] and narrowing of hypothalamic thermoneutral range are possible mechanisms for VMS [21,27]. Reduced circulating serotonin, increased norepinephrine and low estrogen concentrations are implicated in the narrowing of the thermoneutral range [27-29]. The ensuing exaggerated heat loss response with enhanced peripheral vascular reactivity causes

Table 2 Summary of effects of physical exercise on menopause-related health problems.

Problem	Effects
Changes in body composition	• Prevents weight gain • Improves body composition by increasing lean body mass • Reduces body weight and body fat • Promotes development of muscle strength and functional capacity
Cardiovascular disease	• Modifies risk factors of cardiovascular disease • Reduces blood pressure • Improves dyslipidaemia • Improves vascular function • Improves in glycaemic control and insulin resistance • Antioxidant and anti-atherogenic effects • Reverses endothelial dysfunction • Improves coronary blood flow in subjects with coronary artery disease • Promotes endothelium-dependent vasodilation in healthy subjects
Vasomotor symptoms	• Evidence inconclusive
Osteoporosis	• Improves bone mass • Reduces the fracture risk

vasodilatation, resulting in sweating and skin flushing [21,30]. Low sympathetic vasoconstrictor activity, high sympathetic vasodilator activity or other potential mechanisms such as modulation by serotonin and norepinephrine [22] may lead to vascular hyperreactivity [21]. Fluctuations in luteinizing hormone (LH) levels during menopausal transition [22] and reduction in hypothalamic and peripheral β-endorphin levels linked to estrogen deficiency may also play a role in causing VMS [28,31].

Osteoporosis

Estrogen deficiency is the primary factor interfering with normal bone remodeling and leading to osteoporosis in postmenopausal women. Though estrogen insufficiency increases both bone formation and resorption, bone resorption is the predominant effect leading to low bone mass and quality [32]. Increased secretion of osteoclastogenic cytokines such as inteleukin-1 (IL-1), inteleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [32,33], imbalance of receptor activator of nuclear factor αB ligand /Osteoprotegerin (RANKL/OPG) gene expression [34], and inhibition of osteoclast apoptosis [35,36] are some suggested mechanisms. Decrease in progesterone [37], androstenedione and androstenedione/SHBG ratio38 and inhibin A and B [38] are possible hormonal contributors to postmenopausal osteoporosis. Though a significant correlation between follicle stimulating hormone (FSH) and bone resorption has been found [39], a recent interventional study revealed that FSH does not regulate bone resorption in postmenopausal women [40].

Age-related bone loss is an independent risk factor for postmenopausal osteoporosis. Aging is associated with raised levels of reactive oxygen species (ROS) [32,41]. ROS along with high levels of osteocyte derived glycoprotein (sclerostin) inhibit osteoblast proliferation and activity via antagonizing Wnt-β catenine signaling pathway [42]. Increased serum parathyroid hormone (PTH) and diminished IGF-I levels seen with aging [32] and age-related decline in physical activity also contributes to postmenopausal osteoporosis. Reduced mechanical loading lessens the deformation of bones and fluid shear forces on the skeleton, decreasing the molecular signals which activate bone remodeling processes [43].

Impact of Physical Activity and Exercise Training (Table 2)

Changes in body composition

Regular physical activity is beneficial in preventing weight gain, improving body composition, strength development and functional capacity. In a review of exercise in postmenopausal women, a more optimal body composition, including lower adiposity and higher lean mass, was associated with higher levels of physical activity [44]. Regular exercise of any type, even activities such as brisk walking, reduces body weight and body fat [45,46]. Resistance training, preferentially at high intensity, appears to be the most appropriate physical exercise modality to improve muscle mass [47]. Therefore, postmenopausal women would maximally benefit from combining daily aerobic activity with a resistance training programme [44,48].

Regular physical activity causes metabolic adaptations in skeletal muscle, possibly promoted by cumulative effects of transient gene responses to exercise sessions. Repeated, episodic bouts of muscle contraction cause functional adaptation and remodeling in muscle [49]. Training-induced adaptations include changes in contractile proteins, mitochondrial function, metabolic regulation, intracellular signaling and transcriptional responses [49]. Molecular adaptations involve a gradual alteration in protein content and enzyme activity acting through activation and/or repression of specific signaling pathways that regulate transcription and translation, and exercise-responsive gene expression. These include genes which are myogenic regulators, genes of carbohydrate and lipid mobilization, transport and oxidation, mitochondrial metabolism and oxidative phosphorylation, and transcriptional regulators of gene expression and mitochondrial biogenesis [49].

Cardiovascular disease

Regular physical activity and exercise offers cardiovascular protection in both genders in all age groups by modifying the CVD risk factors and improving vascular function. Evidence is scarce as to whether physical activity and exercise influence the increased CVD risk posed by menopausal transition per se. A systematic review of randomized controlled trials (RCT)s in postmenopausal women concluded that a combination of aerobic and resistance exercise may improve hypertension and dyslipidaemia [44]. Interventional trials in postmenopausal women with aerobic exercise alone, resistance training alone and a combination of aerobic exercise and resistance training have shown improvements in lipid profile including the lowering of total cholesterol, triglycerides and low density lipoprotein–cholesterol (LDL-C), increase of high density lipoprotein–cholesterol (HDL-C) and improvements in glycaemic control and insulin resistance [50-52]. Exercise training has been shown to be an effective antioxidant and anti-atherogenic therapy in relation to CVD risk and disease [53-55].

Exercise training reverses endothelial dysfunction and improves coronary blood flow in subjects with coronary artery disease [56,57] and promotes endothelium-dependent vasodilation in healthy subjects [58-61]. Aerobic exercise training in pre and postmenopausal women of comparable ages decreased diastolic blood pressure and increased biomarkers of vascular function i.e., soluble ICAM-1, VCAM-1, and plasma and skeletal muscle endothelin levels [62]. Although there is a dose-response effect between physical activity and reduced CVD risk and disease, even less-vigorous exercise such as walking reduces CVD risk in postmenopausal women [63,64].

Vasomotor symptoms

Exercise appears to have varying effects on VMS. A Cochrane database systematic review of six RCTs found insufficient evidence to support exercise in the management of VMS [65]. Other RCTs [66], longitudinal studies [67] and cross sectional studies [68,69] have described similar findings. Two systematic reviews on the effectiveness of yoga for menopausal symptoms [70,71] and a more recent RCT [72] revealed no significant impact of yoga on VMS. Contrastingly, a recent review concluded that physical activity and structured exercise reduced VMS [73]. Other studies support this finding, showing that both short bouts of exercise and prolonged aerobic training improved VMS to varying degrees [74,75]. A recent RCT reported a significant improvement in VMS in participants of weekly 90-minute yoga classes combined with daily at-home practice compared to subjects engaged in individualized facility-based aerobic exercise training 3 times a week [76].

Several plausible mechanisms explain the effects of physical exercise on VMS. Vagal tone increases as a response to aerobic exercise training [77]. With exercise training, 24-hour urinary norepinephrine decreases, possibly due to increased vagal tone [24]. The influence of stress hormones such as cortisol and catecholamines that could precipitate hot flushes may be counteracted by parasympathetic activation during exercise training [24]. Hypothalamic and peripheral β–endorphin production is increased during exercise and basal β–endorphin levels are higher in active individuals [31]. Higher endorphin levels decrease the frequency and amplitude of LH levels and regulate gonadotropin-releasing hormone (GnRH) levels [31]. Such effects are postulated to stabilize the thermoregulatory centre and reduce the incidence of VMS [24,31]. In women who exercise regularly, the habituation to increased heat and sweating, feeling good and the distraction provided by exercise may contribute to less reporting of hot flushes [24]. As high body mass index [78], and increased adipose tissue may exacerbate VMS by possibly increasing insulation and reducing heat dissipation [19], exercise, by decreasing adipose tissue and body mass index could improve VMS [31].

Osteoporosis

Exercise has the potential to improve bone mass and reduce the fracture risk in postmenopausal women. The positive effects of exercise regimens vary widely although physical activity of any type improves bone health [79]. High-impact loading, low repetition exercises are favored to low-impact loading, high repetition exercises [80]. Mechanical loading decreases serum sclerostin levels [81] thereby mediating osteogenic effects via the Wnt/β-catenine signaling system.

As peak load is the most important factor affecting bone mineral density (BMD) [82], resistance training exercises are the best to improve or maintain bone mass. Resistance training programs, regardless of intensity and frequency, are effective in improving BMD of proximal femur and lumbar spine, although not effective in improving the total body BMD [83]. A Cochrane review of 43 RCTs has shown that lower limb resistance training exercises are the most effective type to improve BMD of the neck of femur, confirming that benefits are site-specific [84].

Aerobic exercises, especially walking, appear to be the most common and preferred exercise in older adults, but they have limited potential in improving bone mass as they provide minimal loading on the skeleton. A review of 12 trials of aerobic training concluded that aerobic exercises retard bone loss without significant improvements of BMD [80]. A significant reduction in biochemical markers of bone resorption was observed following 60 minutes of brisk walking, which supports this finding [85]. Muscle contractions during exercise increase mechanical stresses on bone which in turn enhance the fluid shear forces which are translated into biochemical signals that induce osteogenesis. Bergström et al. have shown a significant increase in osteoprotegerin following one year of aerobic training exercises in postmenopausal women indicating the role of RANK/RANKL/OPG system [86]. Combining aerobic exercises such as walking with high impact exercises such as jogging or stepping are therefore recommended to optimize benefits.

Whole body vibration (WBV) exercise is an alternative for older postmenopausal women, intolerant to other forms of exercise. Acute vibration stimuli transmitted to bone and muscle produce an osteogenic response by changing the flow of bone fluid through direct bone stimulation or indirectly through neuromuscular activation, increasing bone mass and strength. Most studies have shown that WBV is effective in increasing or preventing a

decline in BMD [80], except for a few studies reviewed by Cheung and Giangregorio demonstrating no benefit [81]. A recent RCT showed that 6 months of high-frequency, high-magnitude WBV, significantly increased the BMD of the lumbar spine [87].

Conclusions

Most health problems in women after midlife are linked to the declining estrogen levels, contributed to by physical inactivity, dietary deficiencies, and other changes associated with ageing. Though the key factor responsible for menopause-related health problems appears to be low estrogen levels, decreased progesterone, androstenedione, androstenedione/SHBG ratio, inhibin A and B, increased androgen: estrogen ratio, and changes in other hormones such as cortisol, norepinephrine and IGF-1 are implicated in the pathophysiology. These lead to adverse outcomes such as release of inflammatory mediators, enhanced vascular reactivity, endothelial proliferation, narrowed thermoneutral zone of hypothalamus, fat redistribution, visceral adiposity, sarcopenia, increased CVD risk and accelerated bone loss, contributing to health problems in postmenopausal women.

Physical activity and exercise training are beneficial in postmenopausal women as they exert positive influences on the pathophysiology of menopause-related health problems, especially body composition changes, increased CVD risk and osteoporosis. The benefits occur through diverse mechanisms, e.g. decreased inflammatory mediators, increased activity of anti-oxidants, improvement in endothelial dysfunction, modulation of gene transcription, enhanced vagal tone and endorphin release. An exception is VMS, which is unique to menopausal transition. Exercise appears to have no consistent benefit in alleviating VMS, but VMS is self-limiting and is not associated with serious health consequences. The optimal type of exercise for each condition varies. Resistance training preferentially increases muscle and bone mass, promotes strength development and improves functional capacity, whereas aerobic exercise is more beneficial for the reduction of CVD risk. Thus postmenopausal women should be encouraged to participate in multicomponent exercises combining aerobic exercise and resistance training. Yoga, WBV and any other form of exercise are also encouraged as any increase in the level of physical activity provides health benefits in postmenopausal women.

Though this review reveals that exercise has predominant positive outcomes, variations in findings may be due to reasons such as the differences in study designs, study populations, inclusion criteria, tests and tools used, type, duration and intensity of exercise and different outcome measures. Such inconsistencies can be avoided in future by having well-designed studies harmonizing the type of exercise and the assessment methods, and using similar methodologies to assess each parameter. It is also necessary to design trials suited to clarify uncertainties in pathophysiology, enabling researchers to link pathophysiology to observed outcomes. Therefore, future research should be aimed at designing exercise prescriptions specifying the optimum type, duration, frequency and the period of training to combat osteoporosis, changes in body composition, improvement of CVD risk, alleviate VMS and improve the overall quality of life in postmenopausal women.

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