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REVIEW

Effects of exercise on circulating levels of sex hormones in overweight and obese postmenopausal women: A systematic review

Effets de l'exercice sur les taux circulants d'hormones sexuelles chez les femmes ménopausées en surcharge pondérale : une revue systématique

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Summary
Objective. — This study aimed to examine the evidence regarding the regulatory role of exercise in circulating levels of sex hormones in overweight and obese postmenopausal women.
News. — Exercise has shown to be an effective non-pharmacological tool in obesity and breast cancer prevention. Sex hormones have been proposed as a potential link by which exercise may modulate obesity and breast cancer after menopause, however, the response of sex hormones as a metabolic pathway responsible for the connection between both pathologies

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are not entirely understood. An extensive search was performed using PubMed, Medline, Scopus and SPORTDiscus databases for the period from inception of each database to May 2018. A total of 778 studies were found in the search. Of these, 9 met the inclusion criteria and were further analyzed. Despite the different exercise protocols performed, most studies found a decrease in circulating levels of estrone and estradiol, and an increase in sex hormone-binding globulin (SHBG). However, when the effect of exercise on these sex hormones was compared to an unexercised control group, conflicting results were obtained. A reduction in body mass was reported in those studies in which exercise caused a significant effect on estrone, estradiol and SHBG compared to a control group.
Conclusion. — These results suggest that exercise-induced weight loss and the type of exercise performed may to be critical factors in the modification of the circulation expression of some sex hormones. Further studies are required to elucidate the most effective exercise dose to restore sex hormones homeostasis as potential obesity-breast cancer nexus in the postmenopausal woman.

MOTS CLÉS
Activité physique ;
Ménopause ;
Vieillissement ;
Masse grasse ;
Cancer

Résumé
Objectif. — L'objectif de cette étude était de faire le point de la littérature scientifique sur l'influence de l'exercice sur les taux circulants d'hormones sexuelles chez les femmes ménopausées en surcharge pondérale.
Contexte. — L'exercice s'est avéré être un outil non pharmacologique efficace pour la prévention de l'obésité et le cancer du sein. Il a été suggéré que les hormones sexuelles étaient impliquées dans ce mécanisme, mais ces interactions entre obésité, activité physique et cancer restent incomplètement comprises. Une recherche approfondie a été effectuée en utilisant les bases de données PubMed, Medline, Scopus et SPORTDiscus pour la période allant de la création de chaque base de données à mai 2018. Un total de 778 études ont été trouvées lors de cette recherche. Parmi ceux-ci, 9 répondaient aux critères d'inclusion et ont été analysées en plus en détail. Malgré les différents protocoles d'exercice, la plupart des études ont montré une diminution des taux circulants d'estrone et d'estradiol ainsi qu'une augmentation de la SHBG (protéine porteuse des hormones sexuelles). Cependant, lorsque l'effet de l'exercice sur ces hormones sexuelles a été comparé à un groupe contrôle, des résultats contradictoires ont été obtenus. Une réduction de la masse corporelle a été rapportée dans les études où l'exercice a eu un effet significatif sur l'estrone, l'estradiol et la SHBG en comparaison à un groupe contrôle.
Conclusion. — Les résultats suggèrent que la perte de poids induite par l'exercice et le type d'exercice effectué peuvent être des facteurs critiques dans la modification de l'expression des hormones sexuelles circulantes. D'autres études sont nécessaires pour élucider la dose d'exercice qui serait la plus efficace pour restaurer l'homéostasie des hormones sexuelles en tant que lien potentiel entre l'obésité et le cancer du sein chez la femme ménopausée.

1. Introduction

Obesity and breast cancer are two major diseases that have shown a strong relationship during menopause [1]. However, the physiological pathways responsible for that connection remains to be understood. Sex hormones may be a plausible mechanism to connect both pathologies [2,3], and exercise-induced sex hormones homeostasis restoration may act as an effective non-pharmacological strategy to reduce fat mass accumulation and reduce cancer diagnosis [4—6].

Obesity diagnosis has shown to increase breast cancer risk by 30—50% [7]. In fact, excessive fat mass accumulation is associated with aggressive tumour development and higher resistance to cancer treatment [8]. Besides, in breast cancer survivors, the mortality risk is affected by an increased fat mass accumulation [9]. Hence, the understanding of the physiological mechanisms that may allow linking obesity and breast cancer is required to improve the prevention and treatment of both diseases during menopause [6,10].

Sex hormones regulation is a plausible physiological pathway that may explain the relationship between obesity and breast cancer, a mechanism that gains relevance after menopause [5]. During menopause, adipose tissue is the main responsible for estrogen production through the aromatization of androgens [11]. This aromatization process implies a pronounced reduction in the expression of some sex hormones which produces detrimental effects on

several tissues such as skeletal muscle, liver or adipose tissue [12,13]. In contrast, fat mass accumulation increases sex hormones production via activation of two enzymes: aromatase and 17β-hydroxysteroidase hydrogenase [12—14]. However, the up regulation of sex hormones caused by an excessive fat mass accumulation has also reported being detrimental to some tissues as well as to increase the risk of breast cancer diagnosis [5,15,16]. Therefore, the restoration of sex hormones homeostasis is an imperative task for postmenopausal women to avoid the damaging effects that may cause the down or up regulation of these hormones.

In this regard, exercise is a non-pharmacological strategy in obesity prevention and treatment [17]. Several exercise interventions have reported to improve insulin sensitivity [18,19], as well as to cause a reduction in fat mass accumulation [20] and tumor development [21] in processes mediated by inflammatory biomarkers [22—24]. In contrast, the lack of physical activity has been shown as one of the major risk factors for obesity and breast cancer [24]. Nevertheless, despite this evidences, the regulatory role of exercise on sex hormones production as obesity-breast cancer nexus remains elusive [6,25].

Therefore, this systematic review aimed to examine whether exercise regulates circulating levels of sex hormones in obese and overweight postmenopausal women and to ascertain the most accurate dose of exercise to stimulate the restoration of sex hormones homeostasis.

2. Methods

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [26].

2.1. Search strategy

A search was carried out in Medline, PubMed SPORTDiscuss and Web of Science databases, including articles published until 30 July 2017. The strategy used was: exercise OR physical activity AND obesity AND breast cancer AND progesterone OR estrogen OR androgen, and limits were set to include studies performed in humans and published in English language.

2.2. Study selection, inclusion and exclusion

Articles were included when involved postmenopausal women (> 45 years) overweight or obese ($\geq 25\,kg/m^2$) who performed an exercise or physical activity intervention. Likewise, studies were excluded when participants were treated with hormone replacement therapy (HRT) or were diagnosed with cancer.

2.3. Data extraction and synthesis

The following information was obtained from each study: authors, date of publication, sample size, participant characteristics, training intervention (type, volume, intensity and duration) and circulating expression of sex hormones (progesterone, estradiol, estrone, testosterone, dehydroepiandrosterone (DHEA) and androstenedione), and sex hormone-binding globulin (SHBG).

Circulating expression of sex hormones in response to each exercise intervention (pre- vs. postexercise) was shown as mean of the differences [range].

3. Results

The flow diagram of the systematic review performed is illustrated in Fig. 1. Initially, the database search produced 778 articles, 729 of which were eliminated after title and abstract examination. The full text was retrieved for 49 articles, and 9 satisfied the inclusion criteria.

3.1. Gestagens

3.1.1. Progesterone

The effect of exercise on the circulating expression of progesterone was analysed in 1 study [27]. Sedentary and obese postmenopausal women, 55 (45 to 65) years, were involved. Participants performed 12 weeks of unsupervised endurance training, which consisted of 5—7 sessions/week of 40—45 min/session at 65—80% of maximum heart rate (HR_{max}). No differences were found in the circulating levels of progesterone in response to the exercise intervention [27].

3.2. Estrogens

The effect of exercise on the circulating expression of estrogens was analysed in 8 studies (Table 1). Sedentary and obese postmenopausal women, 62.5 (50—75) years, were involved in these studies [27—33]. Also, a non-obese postmenopausal women group was included in two studies [30,31].

Endurance training was the type of exercise used in 7 of the 8 studies analysed [15,27—32], while endurance and resistance training combination was performed in the remaining study [33]. The exercise program was unsupervised in 3 studies [27—29], whereas a combination of supervised and unsupervised strategy was utilized in the remaining studies. The duration of the exercise program was 12 months in 5 of 8 studies [15,29—32], while the remaining 3 studies showed a duration of 24, 14 and 12 weeks [27,28,33]. The frequency of training was 5 [4 to 7] sessions/week, performing 45 [30 to 60] min/session at moderate/vigorous intensity 75 [60—90] % HR_{max}.

3.2.1. Estradiol

The effect of exercise on the circulating expression of estradiol was analysed in 8 studies. Estradiol expression decreased in response to exercise (−1.64 [−5.39 to 0.4] pg/mL) in 7 of 8 studies (Table 1), only 1 study [27] did not find any significant difference after 12 weeks of an unsupervised endurance exercise intervention. The inclusion of caloric restriction in combination with an exercise program showed that endurance training produced a more pronounced decrease in the circulation levels of estradiol (−3.94 [−9 to −0.6] pg/mL), [15,29] compared to a combination of endurance and resistance training (−0.47 [not

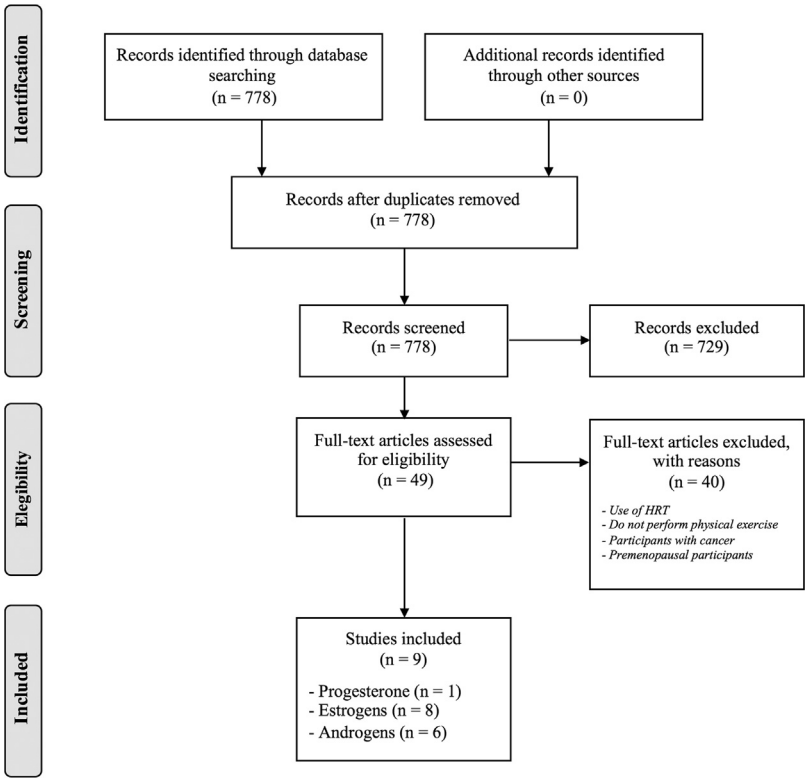

Figure 1 Flow diagram of this systematic review. HRT: hormone replacement therapy.

reported (NR)] pg/ml) [33] or endurance training alone [30—32].

In 6 of 8 studies, the effect of exercise on the circulating levels of estradiol was compared to a control group. Significant differences were reported in half of the studies analysed [15,30,33], no differences were observed in the remaining studies [29,31,32].

3.2.2. Sex Hormone-Binding Globulin (SHBG)

The effect of exercise on the circulating expression of SHBG was analysed in 7 studies. SHBG expression increased in response to exercise in all studies (5.4 [10.39 to 1.11] nmol/L) (Table 1). However, the combination of caloric restriction with either endurance (9.64 [3.8 to 13.7] nmol/L) [15,29] or endurance and resistance training (9.3 [NR] nmol/L) [33] showed a higher increase compared to an endurance training intervention alone (3.21 [−3.8 to 9.8] nmol/L) [30—32].

In 6 of 7 studies, the effect of exercise on the circulating levels of SHBG was compared to a control group. Significant differences were found in the exercise group compared to the control group in 4 studies[15,29,30,33], while no differences were detected in the remaining 2 studies analysed [31,32].

3.2.3. Estrone

The effect of exercise on the circulating expression of estrone was analysed in 8 studies. Estrone expression decreased in 5 of the studies (−1.9 [−3.8 to −0.8] pg/mL). The combination of caloric restriction and endurance training produced the higher diminution in the circulation expression of estrone (−3.8 [−8.6 to 1] pg/mL) [15], compared to either the combination of endurance and resistance training with caloric restriction (−1.4 [NR] pg/mL) [33] or endurance training alone (−1.52 [−9.7 to 6.4] pg/mL) [30—32]. In contrast, estrone did not report any difference in two of the studies [27,31], whereas Choudhury et al. [28] found a non-significant increase after endurance training supervised using questionnaires (1.9 [−53.7 to 57.6] pg/mL).

In 5 of 8 studies, the effect of exercise on the circulating levels of estrone was compared to a control group. No significant differences between groups were found in 4 of the studies [15,30—33], only Campbell et al. [15] observed a significant increase in estrone in the group that performed endurance training and caloric restriction.

3.3. Androgens

The effect of exercise on the circulating expression of androgens was analysed in 6 studies (Table 2). Sedentary and obese postmenopausal women 62.5 [50 to 75] years were involved [15,29,30,33,34], except in 1 study in which a group of non-obese postmenopausal women was also included [30].

Endurance training was the type of exercise used in 5 of the 6 studies analysed, [15,28—30,34] while endurance and resistance training combination was performed in the remaining study [33]. The exercise program was unsupervised in 2 studies [28,29], whereas a combination of a supervised and unsupervised strategy was utilized in the remaining studies [15,30,33,34].

The duration of the exercise program was 12 months in 4 of 6 studies [15,29,30,34], while the remaining 2 studies

Table 1 Effects of exercise on the circulating expression of estrogens in postmenopausal women.

Author	N	Study design	Population	Exercise intervention	Estradiol (pg/mL)	Estrone (pg/mL)	SHBG (nmol/l)
Moreau et al. (2013)	10	RCT	Sedentary obese	Endurance exercise (12 weeks) 5–7 days/week, 40–45 min/session, 65–80% HR_{max}	0 [−18 to 18]	0 [−34 to 30]	–
Kim et al. (2012)	133	RCT	Obese & GI	Endurance exercise + CR (12 months) 5 days/week, 30 min/session, moderate intensity.	−5.39 [−9 to −2]	–	+10.39* [7 to 14]
Friedenreich et al. (2010)	160	RCT	Sedentary obese and non-obese	Endurance exercise (12 months) 5 days/week, 40 min/session, 70–80% HR_{max}	−0.7* [−2.7 to 1.3]	−2.3 [−9.7 to 5.1]	+2.2* [−4.5 to 7.6]
Choudhury et al. (2011)	104	RCT	Sedentary non-obese	Endurance exercise (6 months) Following PAR Questionnaire	−1.9 [−22.3 to 18.5]	+1.9 [−53.7 to 57.6]	+1.1 [−33.3 to 35.5]
Campbell et al. (2012)	117	RCT	Sedentary obese	Endurance exercise + CR (12 months) 5 days/week, 45 min/session, 70–85% HR_{max}	−2.3* [−4.1 to −0.6]	−3.8* [−8.6 to 1]	+8.8* [3.8 to 13.7]
McTiernan et al. (2004)	81	RCT	Sedentary overweight	Endurance exercise (12 months) 5 days/week, 45 min/session, 60–75% HR_{max}	−0.8 [−3.4 to 1.2]	−0.8 [−7.7 to 6.4]	+3.1
Van Gemert et al. (2015)	98	RCT	Sedentary obese	Endurance and resistance exercise + CR (14 weeks) 4 days/week, 60 min/session, 60–90% HR_{max}	−0.47* [nr]	−1.4 [nr]	+9.3* [nr]
Friedenreich et al. (2015)	200	RCT	Sedentary obese and non-obese	Endurance exercise (12 months) 5 days/week, 30 min/session, 60–80% HR_{max}	−0.4 [−1.6 to 0.8]	−1.2 [−5 to 2.6]	+4.2 [−1.4 to 9.8]
Friedenreich et al. (2015)	200	RCT	Sedentary obese and non-obese	Endurance exercise (12 months) 5 days/week, 60 min/session, 60–80% HR_{max}	−0.3 [−1.3 to 0.7]	0 [−3.3 to 3.4]	+3.1 [−3.8 to 9.2]

CR: caloric restrition; GI: Glucose Intolerant; HR_{max}: Maximum Heart Rate; NR: not reported data; PAR Questionnaire: Stanford 7-day Physical Activity Recall Scale; RCT: Randomized control trial.
* $P < 0.05$ vs. control group.

showed a duration of 14 and 24 weeks [28,33]. The frequency of training was 5 [4 to 7] sessions/week, performing 45 [30 to 60] min/session at moderate/vigorous intensity 75 [60–90] % HR_{max}.

3.3.1. Testosterone

The effect of exercise on the circulating expression of testosterone was analysed in 6 studies. Testosterone expression decreased in 5 of the studies (−1.2 [−3.3 to −0.3] ng/dL) (Table 2). The combination of caloric restriction and endurance training produced the higher diminution in the circulation expression of testosterone (−2.41 [−12 to 5] ng/dL) [15,29] compared to either the combination of endurance and resistance training with caloric restriction (−1.4 [NR] ng/dL) [33] or endurance training alone (−0.49 [−6.9 to 5.7] ng/dL) [30,34].

The effect of exercise on the circulating levels of testosterone was compared to a control group in the 6 studies. No significant differences were found in 5 of these studies [29–31,33,34], while Campbell et al. [15] observed a significant increase of testosterone expression in the group that performed endurance training and caloric restriction.

3.3.2. Dehydroepiandrosterone (DHEA)

The effect of exercise on the circulating expression of DHEA was analysed in 3 studies. DHEA expression decreased in all studies (−0.26 [−0.31 to −0.2] ng/mL) (Table 2) in response to endurance training and caloric restriction

Table 2 Effects of exercise on the circulating expression of androgens in postmenopausal women.

Author	N	Study Design	Population	Exercise intervention	T (ng/dL)	DHEA (ng/mL)	AD (pg/mL)
Kim et al. (2012)	133	RCT	Obese & GI	Endurance exercise (12 weeks) 5–7 days/week, 40–45 min/session, 65–80% HR_{max}	−3.3[−12 to 5]	−0,31[−0.5 to −0.1]	–
Friedenreich et al. (2010)	160	RCT	Sedentary obese and non-obese	Endurance exercise (12 months) 5 days/week, 40 min/session, 70–80% HR_{max}.	−0.6	–	−3
Choudhury et al. (2011)	104	RCT	Sedentary non-obese	Endurance exercise (6 months) Following PAR Questionnaire	−0.3[−19.4 to 18.8]	−0,2[−2.6 to 2.6]	−6,7[−422,3 to 408,9]
Campbell et al. (2012)	117	RCT	Sedentary obese	Endurance exercise + CR (12 months) 5 days/week, 45 min/session, 70–85% HR_{max}	−1.4*[−5 to 2,2]	–	−19[−93 to 56]
McTiernan et al. (2004)	81	RCT	Sedentary overweight	Endurance exercise (12 months) 5 days/week, 45 min/session, 60–75% HR_{max}	−0.3[−3.8 to 3.1]	−0.26[−0.81 to 0.27]	−53[−128 to 22]
Van Gemert et al. (2015)	98	RCT	Sedentary obese	Endurance and RE + CR (14 weeks) 4 days/week, 60 min/session, 60–90% HR_{max}	−1.4[nr]	–	−85[nr]

AD: androstenedione; CR: caloric restriction; GI: glucose intolerant; HR_{max}: Maximum Heart Rate; NR: not reported data; PAR Questionnaire; Stanford 7-day Physical Activity Recall Scale; RCT; Randomized control trial; RE; resistance exercise; T; testosterone.
* $P < 0.05$ vs. control group.

(−0.31 [−0.5 to −0.1] ng/mL [29], endurance training alone (−0.26 [−0.81 to 0.27] ng/mL [34], and when exercise was monitored by questionnaires (−0.2 [−2.6 to 2.6] ng/mL [28].

The effect of exercise on the circulating levels of DHEA was compared to a control group in the 3 studies, and no significant differences were reported in any of the studies analysed [28,29,34].

3.3.3. Androstenedione

The effect of exercise on the circulating expression of androstenedione was analysed in 5 studies. Androstenedione expression decreased in the 5 studies (−28.6 [−85 to −3] pg/mL) (Table 2), in response to the combination of caloric restriction with endurance training (−19 [−93 to 56] pg/mL) [15] or endurance and resistance training (−85 [NR] pg/mL) [33], as well as in response to endurance training alone (−19.8 [−141 to 135] pg/mL) [30,34].

The effect of exercise on the circulating levels of androstenedione was compared to a control group in 4 of the 5 studies, and no significant differences were reported in any of these studies [15,28,30,33,34].

4. Discussion

The present systematic review investigates the role of exercise as a regulator of the circulating expression of sex hormones in obese and overweight postmenopausal women.

Chronic doses of exercise (from 12 weeks to 12 months) stimulates a reduction of the circulating expression of estradiol, estrone, testosterone, DHEA and androstenedione and an increase SHBG expression; however, only the response of estrogens to exercise reported a significant difference compared to control groups. Moreover, the combination of endurance training and caloric restriction intervention showed the higher weight loss and stimulate a more pronounced modulation of the circulating levels of sex hormones, suggesting the relevance of exercise-induced weight loss and the type of exercise as two critical factors in the restoration of sex hormones homeostasis.

Fat mass accumulation produces an imbalance in insulin sensitivity, inflammation and sex hormones production, which stimulate the risk of breast cancer diagnosis in postmenopausal women [35,36]. During menopause, sex hormones production is altered which in some cases has shown to promote adverse effects [5,12,13,15,16]. Thus, the identification of a non-pharmacological intervention that may restore sex hormones homeostasis is essential in this population.

In this regard, exercise has shown to be an effective tool to prevent and protect postmenopausal women from obesity and breast cancer prevalence [24]. However, the ability of exercise to regulate sex hormones as a nexus between these two diseases has not been fully investigated. The present review shows that endurance training alone or in combination with caloric restriction produced the higher alteration

of sex hormones, stimulating a decrease in the circulating expression of estradiol, estrone, testosterone, DHEA and androstenedione, and an increase in SHBG [15,28—34]. However, only the alteration of estrogens expression reported being significant when compared to an unexercised control group. Therefore, this data suggests the role of fat mass reduction and the type of exercise as two key factor to interpret the circulating expression of estrogens during menopause.

Fat mass accumulation produces an upregulation of estrogen expression due to an increased activation of the aromatization process during menopause [36,37]. This fact supports the reduction in circulating levels of estrogens, and to a lesser extent of androgens, in response to exercise-induced weight loss interventions. Hence, the modification of the circulating expression of estrogens observed in this review may be attributed to a reduction in total fat mass.

Interestingly, endurance training was more effective than a combination of endurance a resistance training when both interventions included caloric restriction [15,29,33]. Since resistance exercise is a well-recognised anabolic and anti-atrophic stimulus, [38] the attenuated reduction in estrogens observed in those interventions in which resistance training was included in the exercise protocol may indicate a role of skeletal muscle in the regulation of estrogens availability in blood.

Muscle protein synthesis is driven by a damage/repair process that occurs after 1—2 weeks of resistance training [39]. Estrogen presence in skeletal muscle has been associated with damage/repair process in this tissue [40,41] by decreasing neutrophil invasion into damaged muscle fibers [40]. In fact, 17β-estradiol and the estrogen receptors beta (ERβ) are associated with an attenuation of protein degradation in skeletal muscle [42—45] promoting regenerative and anti-apoptotic effects in this tissue through a mechanism that involves satellite cells [46]. This evidence may lead to suggest that in a population of postmenopausal women, the decrease in the circulating levels of estrogen may be attributed to skeletal muscle, which may uptake these sex hormones with remodelling purposes in response to resistance exercise. Nonetheless, the implication of other tissues and functions in the regulation of the availability of the circulating levels of estrogens in response to exercise cannot be avoided.

Although several studies have evaluated the effects of exercise on the circulating levels of estrogens, there is a lack of evidence regarding the expression of estrogen receptor alpha (ERα), related to breast cancer progression and development, and estrogen beta-receptor (ERβ), implicated in protein synthesis/degradation of skeletal [47,48]. The understanding of ERα and ERβ expression in response to exercise may help to interpret the role of estrogen in the metabolism of several cell types (e.g., adipocyte, myocyte and the tumour cells) since these two receptors regulate the availability and production of estrogens.

In conclusion, the present systematic review shows that exercise-induced weight loss regulates the expression of circulating estrogens in overweight and obese postmenopausal women. The pronounced reduction of estrogen expression observed in response to endurance training compared to endurance plus resistance training also suggest that the type of exercise may be a critical factor to understand the exercise-induced regulation of the circulating expression of sex hormones. Further studies are required to identify the most effective exercise dose (intensity, volume, frequency and progression) to restore the homeostasis on the circulating levels of sex hormones and the expression of estrogen receptors.

Ethical statement

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure of interest

The authors declare that they have no competing interest.

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