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Ovariectomized rodents as a menopausal metabolic syndrome model. A minireview

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Abstract

Bilateral ovariectomy is the best characterized and the most reported animal model of human menopause. Ovariectomized rodents develop insulin resistance (IR) and visceral obesity, the main risk factors in the pathophysiology of metabolic syndrome (MS). These alterations are a consequence of hypoestrogenic status, which produces an augment of visceral fat, high testosterone levels (hyperandrogenism), as well as inflammation, oxidative stress, and metabolic complications, such as dyslipidemia, hepatic steatosis, and endothelial dysfunction, among others. Clinical trials have reported that menopause per se increases the severity and incidence of MS, and causes the highest mortality due to cardiovascular disease in women. Despite all the evidence, there are no reports that clarify the influence of estrogenic deficiency as a cause of MS. In this review, we provide evidence that ovariectomized rodents can be used as a menopausal metabolic syndrome model for evaluating and discovering new, safe, and effective therapeutic approaches in the treatment of cardiometabolic complications associated to MS during menopause.

Keywords Ovariectomy · Menopause model · Metabolic syndrome · Hypoestrogenism

Introduction

The sex-bias in basic and clinical research and the vulnerability of menopausal women

Sex is the main determinant of our physical attributes, the structure of our brains, our behavior, the susceptibility, progression, and response to diseases, and our own conception of self [1]. Despite this sexual identity, biomedical scientists have ignored the clear and important differences between males and females [2], i.e., analysis of the scientific literature in numerous disciplines shows that there is an indisputable sex-bias: "males are studied much more than females, in both animal and human research". In fact, drug development is based on research on males, even for diseases that are more frequent in females, and despite evidence that drug metabolism and efficacy differ in the two sexes [1]. For this reason, the National Institutes of Health in the United States recently ordered the inclusion of both sexes in clinical trials and basic research [3], with the aim of promoting gender-specific therapies that can contribute to developing individualized therapies in the future [2].

Sexual identity is highly influenced by hormones. Hormones are the most amazing molecules in biochemistry, i.e., they are the only ones that can achieve the formation, growing, differentiation, functioning, behavior, and reparation of an entire organism, acting at minimal concentrations [4–7]. Moreover, sex hormones are responsible for sexual differentiation (phenotype and behavior), and participate importantly in the maintenance of metabolic homeostasis [8, 9]. Among sex hormones, estrogens distinguish themselves for their protector role on cardio-metabolism, playing a very important function in the regulation of body fat distribution, and maintenance of metabolic health through several mechanisms, like (1) reduction in food intake maintaining an anorexigenic tone and improving satiety signals [10, 11], (2) regulating body fat distribution, favoring the subcutaneous and gluteal-femoral fat depot and preventing the

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visceral storage [10, 12], (3) promoting browning of adipose tissue, increasing the catabolism of fatty acids and glucose [10, 13, 14], while improving insulin and leptin sensitivity [15, 16], (4) acting as anti-inflammatory and antioxidant agents that prevent endothelial dysfunction, vascular inflammation and atherosclerosis [17–21], and (5) stimulating the release of calcitonin gene-related peptide (CGPR) from perivascular nerves, and nitric oxide production in blood vessels promoting anti-hypertensive actions [22–24] (Fig. 1). Considering all these positive effects of estrogens on cardio-metabolism, it seems reasonable to suppose that a hypoestrogenic state could promote the development of metabolic syndrome (MS) through several mechanisms, like visceral obesity development, and the resulting inflammatory and oxidative states, which together with atherogenic dyslipidemia contributes and/or aggravates a simultaneous

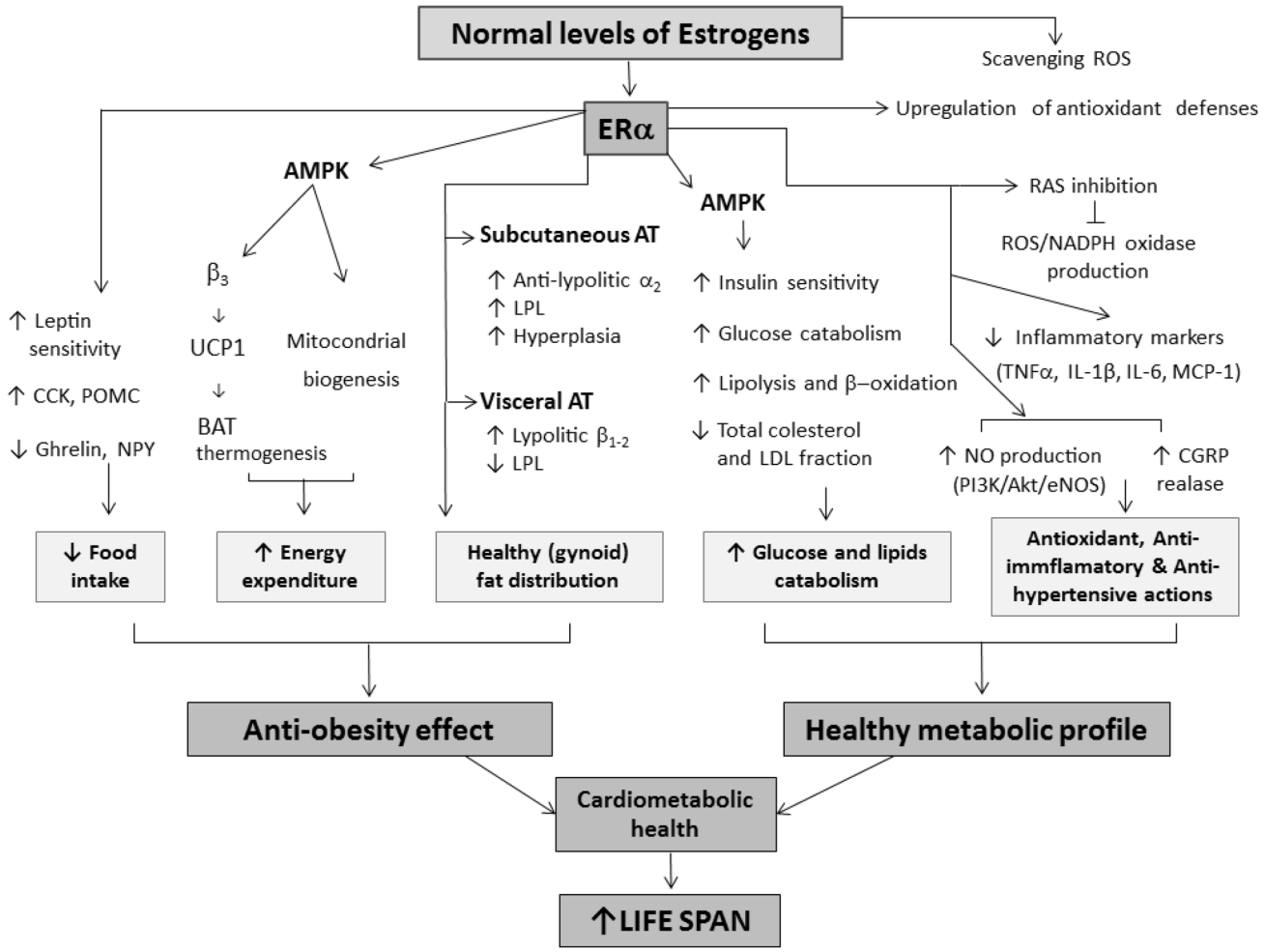

Fig. 1 Estrogen pathways for metabolic regulation and body weight maintenance. Acting mainly by estrogen receptors alpha (ERα), estrogens reduce food intake increasing leptin sensitivity, and the potency of anorectic signals like cholecystokinin (CCK) and pro-opiomelanocortin (POMC), at the same time estrogens reduce the signaling of orexigenic molecules like neuropeptide Y (NPY) and ghrelin, also modulate brown adipose tissue (BAT) thermogenesis through AMPK → β_3 → UCP1 pathway, and promote mitochondrial biogenesis. In subcutaneous adipose tissue (AT), estrogens increase the expression of the antilipolytic α_2 adrenoceptors, and augment the activity of lipoprotein lipase (LPL) promoting the uptake and storage of fatty acids, meanwhile in visceral adipose tissue increase lipolytic $\beta_{1\text{-}2}$ adrenoceptors and reduce LPL activity, increasing lipolysis and preventing the visceral storage of fat in the abdominal cavity. Estrogens, also promote hyperplasic adipose tissue expansion (related with an increase in insulin sensivity) over hypertrofic procces (related to oxidative stress, fibrosis and immflamation). Regarding energetic metabolism, estrogens increase insulin sensitivity improving glucose uptake through specific transporters, and aughmenting glucose catabolism by activation of key enzymes, also increase lipid catabolism by lipolysis and β-oxidation, and reduce total colesterol and LDL fraction, preventing the development of atherogenic dyslipidemia. Estrogens can act as scavengers of free radicals by it self, but their antioxidants effects also are mediated by ERα activation and upregulation of enzymatic and no enzymatic antioxidant defenses, reduction of reactive species oxygen (ROS) production by renin-angiotensin system (RAS)/NADPH oxidase inhibition, and indirectly, promoting a decrease in the expression of iNOS, and levels of inflammatory markers (TNFα, IL-1β, IL-6, MCP-1). Finally, estrogens promote vascular relaxation through PI3K/Akt/eNOS pathway activation and calcitonin gene-related peptide (CGPR) release

development of insulin resistance. All these conditions can lead to endothelial dysfunction and hypertension, which in turn promotes complications such as myocardial infarction and stroke, or the development of other chronic diseases like type two diabetes (T2D), which increase the risk of mortality in menopausal women [11, 15] (Fig. 2). In this way, estrogens have been assigned as main responsible for prolonged life span and cardiometabolic health in premenopausal women, and represent the main biological advantage in nature compared to males.

Among estrogens, 17β-estradiol (E2) is the most abundant and potent in humans [24], its production in females before the hormonal decline mainly occurs in the ovaries after the aromatization of androgenic precursors by aromatase. After estrogenic deficit and in males, estradiol is synthesized in extragonadal sites, such as the adipose tissue, where it acts locally as a paracrine or intracrine factor [12]. The protector effects of estrogens result from their interaction with classical estrogen receptors (ERs), ERα and ERβ, as well as the more recently identified G-protein coupled receptor 30 (GPER30)/G-protein estrogen receptor 1 (GPER1), and exert their actions via both genomic and non-genomic mechanisms [17]. However, the majority of cardiometabolic protector effects for estrogens are mediated by ERα, which is in higher proportion than ERβ in key tissues for metabolic regulation; indeed, estrogen receptor alpha knockout (ERαKO) mice show severe alterations in their metabolism suggesting that the beneficial effects of E2 are mainly mediated by this receptor and not by ERβ since ERβKO mice do not show important alterations in these parameters [11, 15]. Like the other sex hormones, E2 is transported from circulation to target tissues by sex-hormone binding globulin (SHBG), whose diminished concentrations during estrogenic deficiency (menopause, Poly Cystic Ovary Syndrome) are highly related with insulin resistance and MS development [25]. Actually, it has been amply reported that the risk for developing chronic diseases such as central obesity, T2D, hypertension, hepatic steatosis, and cardiovascular disease or MS is higher in males than in females just before estrogenic deficiency, and it is well known that this prevalence shifts during the menopausal transition and after that. Clinical consequences of cardiovascular disease usually manifest 7–10 years later in women than in men when the protector effects of estrogens are lost. In this condition, the risk of metabolic disturbances and cardiovascular events, such as myocardial infarction and stroke, increase importantly and tend to have a more severe prognosis and a higher mortality in women [26–28].

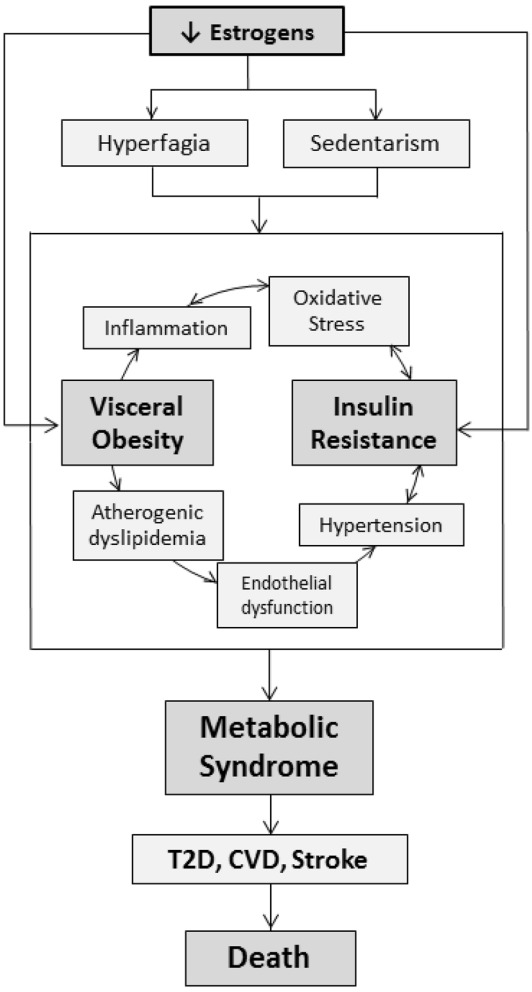

Fig. 2 The reduction of estrogens signaling promotes the development of metabolic syndrome and increases mortality. Hypoestrogenism promotes the development of metabolic syndrome (MS) through visceral obesity development, and the resulting inflammatory and oxidative states, which together with atherogenic dyslipidemia, contributes and/or aggravates a simultaneous development of insulin resistance. All these conditions can lead to endothelial dysfunction, hypertension, cardiovascular disease (CVD), stroke, or type 2 diabetes (T2D), increasing the risk of mortality in menopausal women seriously

Unfortunately, despite menopause and its metabolic and cardiovascular consequences affect all women, some of them for decades, there is not an urgent and priority concern in the agenda of governments' health services or in the research field to face this growing problem [11, 26]. Hence in this review, we propose the use of an animal model that adequately represents the contribution of estrogenic deficiency in the pathophysiology of MS, this model will allow the research and development of new and safe therapeutic strategies for metabolic syndrome during menopause, an increasing public health problem that affects a large segment of the female population.

Metabolic syndrome during menopause

Menopause is an inevitable component of aging in women; it is defined as the permanent cessation of the menstrual cycle owing to the loss of ovarian reproductive function, either occurring spontaneously by follicular atresia or secondary to other conditions such as the removal of the ovaries or chemotherapy [26]. The transition to menopause is characterized by metabolic changes that promote the development of MS [29]. The MS is related to a set of cardiovascular, renal and hepatic risk factors that favor the development of T2D. In general, there is a consensus to obtain a clinically useful definition that includes the presence of at least three of the following factors: abdominal obesity, fasting hyperglycemia, hypertension, dyslipidemia, and insulin resistance [30–33]. Currently, oxidative stress, chronic low-grade inflammation, and a prothrombotic state have also been considered [34–36], as well as a decrease in SHBG [37, 38]. Observational studies have shown that the prevalence of MS is lower in women at reproductive age in comparison with men of the same age. However, this advantage disappears along the transition stage to the establishment of menopause [38, 39], where the incidence of MS increases 2–3fold [40, 41]; even several reports show that cardiovascular risk and mortality for coronary heart disease increase up to 4–5 times in postmenopausal women [42, 43], indicating that the loss of estrogens is fundamental in the development of the main risk factors associated with MS. Accordingly, evidence suggests that estrogenic deficiency in menopause is a predictor of MS independent of aging [43]. These issues are especially important because women will spend at least a third of their lives in a postmenopausal state.

The changes that promote the development of MS during and after the menopausal transition are a consequence of hypoestrogenic status which produces an increase in android body fat, a decrease in muscle mass, and an important predisposition to develop insulin resistance [44–46]; thereby, the increase in visceral adipose tissue contributes to the rise in the production of cytokines and the establishment of a pro-inflammatory state (Fig. 2) [47]. In this regard, when all MS factors are adjusted for age in women, only abdominal obesity and insulin resistance were associated significantly with a postmenopausal status, and it is independent of general adiposity before postmenopausal state [41, 48]. In addition, if women are overweight at the time of entering menopause, there is a higher probability of developing MS over the years [37].

In menopausal women the prevalence of MS is higher in those subjected to ovariectomy, compared with who had natural menopause [49], probably the removal of ovaries in women under 45 years promotes an acute reduction of estrogen that causes the accelerated appearance of menopause, along with the development of obesity, an increase in the production of atherogenic lipoproteins, and oxidation of LDL [50, 51]; there is also an elevation in arterial vascular tone as a consequence of the reduction of vasodilator peptides, and a rise in vasoconstrictor peptides [52]. Likewise, these women have a higher risk of developing T2D and cardiovascular disease compared with their counterparts in the general population [51]. Therefore, the sudden change in the hormonal status resultant from surgery promotes the development of cardiovascular risk factors such as obesity, hypertension, dyslipidemia, and insulin resistance [44, 53, 54]. On the other hand, the decrease in estrogen production during menopause has been associated with increased androgen production (testosterone), which promotes the elevation of blood pressure, triglycerides, and increased risk of developing insulin resistance favoring the manifestation of MS [37, 38, 55]. Notwithstanding, visceral obesity, and hypertriglyceridemia, in addition to the metabolic implications that have in menopause, are also associated with the appearance of other factors, for example, dry skin, depression, and lack of sexual desire [56]. Thus, in summary, menopause is associated with the onset and progression of the main components of MS and other factors that significantly affect the quality of life of women in a hypoestrogenic state.

Inflammatory markers and their involvement in Metabolic Syndrome (MS) development

Inflammation is one of the main risk factors recently considered as a big contributor in the physiopathology of metabolic syndrome; indeed, its role as the link between obesity, insulin resistance, atherogenic dyslipidemia, and cardiovascular disease begins to emerge as a key in the promotion and development of several diseases [57–60]. Obesity promotes a low-grade activation of the innate immune system and the development of inflammation that contributes significantly to the onset of alterations present in MS [57, 58]. The main source of proinflammatory cytokines in MS are adipocytes and macrophages, where the latter may have a change in their phenotype that makes them more proinflammatory, and together with leading to an overproduction of proinflammatory cytokines that initially promote localized inflammation and subsequently propagates to systemic level [57–59]. In this way, adipocytes and macrophages can produce proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and the tumor necrosis factor-alpha (TNF-α) that have been closely associated with the pathophysiology of MS. These proinflammatory cytokines can act paracrine or autocrine manner, promoting their own release through positive feedback that allows them to initiate and maintain the inflammatory state for long periods of time

[59]. The main molecular mechanisms through which IL-1β, IL-6 and TNF-α exert their effects have been mainly associated with the activity of transcription factors such as NF-κB, JNK, and STAT, related with the proinflammatory effects of obesity, development of insulin resistance, and endothelial dysfunction which also have played a central role in the development of metabolic disorders such as T2D [57–60].

Use of estrogenic dysfunction models in the study of factors associated with the metabolic syndrome

Currently, there is a wide need to understand the pathophysiology of various metabolic disorders present in large part of the population worldwide, mainly those associated with MS and T2D. For this reason, it is important to develop animal models that mimic these pathologies and provide information on their development, progression, and prevention. Thereby, experimental models of metabolic alterations induced by the consumption of hypercaloric diets [61], transgenic models, and drugs, especially in rodents, have been widely used to understand their relationship with several alterations associated with MS and its subsequent complications [62, 63]. In this sense, these models allowed to scrutinize a wide variety of diseases related to MS, such as hypertension, cardiomyopathy, atherosclerosis, kidney damage, hepatic steatosis, Alzheimer and insulin resistance [64–69]. Notably, due to the importance of estrogens in metabolism, the use of animal models for loss, deficiency or resistance to estrogens, like ovariectomized rats and mice, aromatase knockout (ARKO) mice, and ERαKO mice has been used to evaluate many of the factors associated with MS (Table 1) [14].

Ovariectomized rats and mice develop the majority of metabolic syndrome risk factors

After ovariectomy, there is an increase in visceral adipose tissue storage, which promotes serious metabolic disturbances that include insulin resistance, dyslipidemia, hyperleptinemia, and lower adiponectin concentrations; these metabolic derangements also occurring during menopause and may trigger cardiovascular disease in women [70]. Supporting this evidence, there are several ovariectomy-induced hypoestrogenic animal models, which reported that ovariectomy per se promotes the development of obesity, glucose intolerance, insulin resistance, atherogenic-dyslipidemia, oxidative stress and inflammation, mimicking the features of the MS during menopause [71, 72]. On the other hand, the estrogenic dysfunction animal models such as the obese ARKO mice [73–75], or the ERαKO mice only develop some of the MS factors, and frequently they must combine with the administration of a hypercaloric diet to promote or aggravate the development of all metabolic syndrome risk factors [14, 76, 77] (Table 1). By this way, is clear that ovariectomy model develop most of the MS risk factors (Fig. 3 and Table 1), which signal it as one of the most representative models of metabolic syndrome during a hypoestrogenic state like menopause.

Ovariectomy as a menopausal metabolic syndrome model

Among those models of hypoestrogenism or menopause are: (1) Natural reproductive senescence, (2) Ovariectomy, and (3) Ovotoxins to accelerate ovarian failure; all are used depending on the stage along with the establishment of menopause that it wants to study [78, 79].

Similar to menopause in women, rodent natural reproductive senescence (estropause) shows a dysregulation in hypothalamic-pituitary–gonadal (HPG) axis, morphofunctional ovarian changes, gonadal hormone fluctuations and irregular fertility [79]. However, only 25% of estropause rodents show a similar hormonal profile with menopausal women, the rest of animals maintain a constant estrus state characterized for high and sustained levels of estradiol and progesterone, contrary to the low levels maintained during menopause [78]. Another important difference between aging female rodents and women is the presence of mature ovarian follicles in estropause rodents, while in menopausal women the ovarian failure is complete [79]. In fact, many researchers finally conduct an ovariectomy in aged rodents to avoid these discrepancies [78]. Additionally, for the high rates of mortality, and because the model needs a long time for implementation, it requires rat strains with high longevity such as the Fischer-344, Sprague Dawley or Long Evans [79].

Other model more recently reported, and implemented is the 4-vinylcyclohexene diepoxide, or VCD, considered as a model of transitional menopause because it selectively depletes the non-growing ovarian follicle pool via atresia, resulting in follicular depletion, and eventual ovarian failure. This model shows an ovarian, and hormone profile more similar to the majority of women undergoing menopause and retain their reproductive organs in the post-reproductive life stage, the animals also present some neurologic and cardiometabolic alterations associated with hypoestrogenic state during menopause. However, its implementation has important disadvantages, in first place, VCD is toxic at high doses, and the regimen of VCD administration requires around fifteen series of intraperitoneal injections ranging from 80 to 160 mg/kg, which also result stressing for the animals, even it was reported a reduction in body weight during injections, another consideration is the elevated costs

Table 1 Studies of metabolic syndrome development into hypoestrogenic state without other treatment. Summary of models used, metabolic syndrome factors present and main pathologies or alterations associated

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present											Pathologies or alterations associated	Tissue/ organ evaluated	Reference
				Ob	IR	Dyslipidemia				HT	HL	OS	Inflammatory markers				
						TC	TG	LDL	HDL				TNF-α	IL-6	IL-1 β		
Rat																	
Wistar	3 Mos.	12 Wks.	Ovariectomy	✓	✓	✓	✓	✓	✓		✓					Pre-diabetic state	Serum, adipose tissue and liver	Tawfik et al. [70]
Wistar	3 Mos.	8 Wks.	Ovariectomy	✓		✓	✓	✓	✓			✓	✓		✓	Pre-diabetic state	Serum and pancreas	Fahmy et al. [71]
Wistar	3 Mos.	8 Wks.	Ovariectomy			✓	✓		✓							Hepatic steatosis and kidney damage	Plasma, liver and kidney	Panneerselvam et al. [96]
Wistar	11 Wks.	8 Wks.	Ovariectomy	✓												Weight gain in menopause.	Serum and adipose tissue	Babaei et al. [102]
Wistar	10 Wks.	16 Wks.	Ovariectomy	✓							✓					Hepatic steatosis	Serum	Pósa et al. [97]
Wistar	8 Wks.	7 Wks.	Ovariectomy	✓	✓	✓	✓									Metabolic disturbance	Serum, liver and adipose tissue	Majumdar et al. [80]
Wistar	6 Wks.	16 Wks.	Ovariectomy	✓			✓					✓				Hepatic steatosis	Plasma, serum and liver	Munhos et al. [103]
Wistar	200-220 g	12 Wks.	Ovariectomy	✓	✓							✓				Cardiomyopathy development	Plasma, serum and heart	Sivasinprasasn et al. [81]
Wistar	200-220 g	12 Wks.	Ovariectomy	✓								✓				Cardiomyopathy development	Heart	Morra et al. [98]

Table 1 (continued)

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present											Pathologies or alterations associated	Tissue/organ evaluated	Reference
				Ob	IR	Dyslipidemia				HT	HL	OS	Inflammatory markers				
						TC	TG	LDL	HDL				TNF-α	IL-6	IL-1 β		
Wistar	200-220 g	8 Wks.	Ovariectomy	✓	✓											Metabolic disturbance	Plasma, serum and heart	Sivasinprasasn et al. [81]
Wistar	Weaning	5 Wks.	Ovariectomy	✓												None	Plasma and heart	Busserolles et al. [104]
Wistar	200-220 g	4 Wks.	Ovariectomy													None	Plasma, serum and heart	Sivasinprasasn et al. [81]
Wistar Kyoto	6 Mos.	8 Wks.	Ovariectomy	✓	✓					✓						Postmenopausal metabolic disturbance	Plasma, liver and aorta	Bitto et al. [105]
Sprague-Dawley	8 Wks.	16 Wks.	Ovariectomy	✓	✓	✓	✓									Kidney damage	Plasma, adipose tissue, liver and kidney	Zhang et al. [65]
Sprague-Dawley	8 Wks.	12 Wks.	Ovariectomy	✓	✓	✓	✓	✓								Hepatic steatosis	Serum, liver and skeletal muscle	Prasannarong et al. [95]
Sprague-Dawley	8 Wks	12 Wks.	Ovariectomy	✓	✓	✓		✓	✓							Metabolic disturbances	Serum, plasma and skeletal muscle	Saengsirisuwan et al. [72]
Sprague-Dawley	8-9 Wks.	10 Wks.	Ovariectomy	✓	✓					✓						Cardiovascular dysfunction	Serum, aorta and heart	Bendale et al. [83]

Table 1 (continued)

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present											Pathologies or alterations associated	Tissue/organ evaluated	Reference
				Ob	IR	Dyslipidemia				HT	HL	OS	Inflammatory markers				
						TC	TG	LDL	HDL				TNF-α	IL-6	IL-1 β		
Sprague-Dawley	180-200 g	12 Wks.	Ovariectomy	✓		✓	✓				✓					Hipoxy in adipose tissue	Serum, adipose tissue	Xu et al. [106]
Sprague-Dawley	8 Wks.	6 Wks.	Ovariectomy	✓	✓											Metabolic disturbance	Serum, adipose tissue and skeletal muscle	Rattanavichit et al. [107]
Sprague-Dawley	5 Mos.	6 Wks.	Ovariectomy	✓												Alterations in estrogen receptor expression	Serum, Skeletal muscle and adipose tissue	Gorres et al. [108]
Sprague-Dawley	6 Mos.	3 Wks.	Ovariectomy	✓		✓	✓	✓								Hepatic steatosis and dyslipidemia	Plasma and liver	Zhang et al. [82]
LCR rats	22 Wks.	27 Wks.	Ovariectomy	✓	✓											Spontaneous physical activity reduction	Adipose tissue and skeletal muscle	Park et al. [109]
Sprague-Dawley	3 Mos.	10 Wks.	Ovariectomy			✓	✓	✓	✓			✓	✓			Atherosclerosis	Serum	Hassan and Abdel-Wahhab [84]
Wistar	200±20 g	12 Wks.	Ovariectomy + supplemented Met diet													Atherosclerosis	Thoracic aorta rings and plasma	Zhen et al. [85]
Wistar	3 Mos.	9 Wks.	Ovariectomy									✓				Atherosclerosis	Coronary arteries	Koyuncu et al. [86]

Table 1 (continued)

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present										Pathologies or alterations associated	Tissue/organ evaluated	Reference
				Ob	IR	Dyslipidemia				HT	HL	OS	Inflammatory markers			
						TC	TG	LDL	HDL				TNF-α	IL-6	IL-1 β	
Withe albino rats	200-250 g	12 Wks.	Ovariectomy + HFD			✓	✓	✓	✓		✓		✓			Atherosclerosis and osteoporosis	Aorta rings and serum	Mohamed et al. [87]
Transgenic mice																		
C57B/6J mice	10 Wks.	12 Wks.	Ovariectomy	✓	✓								✓	✓	✓	Hepatic steatosis and inflammation	Adipose tissue, liver	Rogers et al. [110]
C57B/6J mice	22 Mos.	8 Wks.	Ovariectomy	✓		✓						✓				Hepatic steatosis	Liver and ovary	Valencia et al. [111]
TNFRSF14 -/- Mice	6 Wks.	12 Wks.	Ovariectomy	✓	✓							✓				Inflammatory state	Serum, femora and tibiae bones	Choi et al. [75]
C57BL/6 mice	10 Wks.	12 Wks.	Ovariectomy	✓	✓											Inflammatory state	Serum, liver, adipose tissue, femora and tibiae bones	Choi et al. [112]
MKR mice	6 Wks.	11 Wks.	Ovariectomy	✓		✓					✓					Mammary tumor growth	Serum and mammary tissue.	Ben-Shmuel et al. [113]
ICR Mice	25-30 g	4 Wks.	Ovariectomy													Vascular dysfunction	Plasma, skin and liver	Tominaga et al. [114]

Table 1 (continued)

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present											Pathologies or alterations associated	Tissue/ organ evaluated	Reference
				Ob	IR	Dyslipidemia				HT	HL	OS	Inflammatory markers				
						TC	TG	LDL	HDL				TNF-α	IL-6	IL-1 β		
C57BL/6 mice	10-12 Wks.	90 days	ARKO	✓			✓									Adipocity increase	Serum and gonadal fat	Misso et al. [73]
C57BL/6 mice	Adults	17 days	ARKO	✓							✓					Metabolic dysfunction	Plasma, adipose tissue and uterus	Bader et al. [74]
C57BL/6 mice	18 Wks.	2-8 Wks.	ERαKO	✓	✓	✓	✓				✓	✓				Inflammatory state and metabolic dysfunction	Blood, skeletal muscle, adipose tissue and liver	Ribas et al. [76]
C57BL/6 mice	12-14 Wks.	5 and 12 Wks.	Liver ERαKO + HFD	✓	✓	✓	✓									Metabolic dysfunction	Plasma and liver	Zhu et al. [77]
Chemical model																		
Sprague-Dawley	4-5 Wks.	13 Mos.	Testosterone pump infusion	✓	✓					✓						Renal damage	Blood, plasma and kidney.	Dalmasso et al. [115]
Wistar	3 Wks.	11- 12 weeks	Letrozole pump infusion	✓												Polycystic Ovary Syndrome	Plasma, serum, adipose tissue and ovary	Maliqueo et al. [116]
$B_6C_3F_1$ mice	4 Wks.	17 days	Injection daily VCD			✓										Loss of ovarian function	Blood, plasma and Ovary	Romero-Aleshire et al. [117]
Lewis	18 Mos.	2 weeks	Letrozole													Androgen deficiency	Plasma, liver	Borbélyová et al. [118]

Table 1 (continued)

Specie	Age/BW	Final time	Model used	Metabolic syndrome factors present									Pathologies or alterations associated	Tissue/organ evaluated	Reference
				Ob	IR	Dyslipidemia			HDL	HT	HL	OS	Inflammatory markers		
						TC	TG	LDL					TNF-α	IL-6	IL-1 β
Sprague-Dawley	15 Mos.	13 days	Testosterone pump infusion											Appetite alterations	Serum, hypothalamic tissue	Iwasa et al. [119]

BW body weight, *Ob* obesity, *IR* insulin resistance, *TC* total cholesterol, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *HT* hypertension, *HL* hyperlepticnemia, *OS* oxidative stress, *TNF-α* tumor necrosis factor α, *IL-6* intesssrleukin 6, *IL-1 β* interleukin 1 β, *HFD* high fat diet, *ERαKO* estrogen receptor alpha knockout, *ARKO* aromatase knockout

of implementation since VCD is used in high and repetitive doses [78, 79].

Finally, the model considered as the "gold standard" in the study of hypoestrogenism or menopause is that induced by ovariectomy [79], since it has several advantages over others, among them the easy implementation, cost reduction, rapid manifestation of hypoestrogenism, and the most important, ovariectomy itself is the most effective model of hypoestrogenism in promoting the development of the main risk factors of MS, compared to the natural senescence or chemical models that present the development of few MS factors. i.e.; ovariectomy promotes the development of visceral obesity, insulin resistance, oxidative stress, inflammation, atherogenic dyslipidemia, hepatic steatosis and hypertension [71, 80–83] (Table 1). Ovariectomized rats also develop other complications present in menopausal women like atherosclerotic lesion [84–87], osteoporosis, and cognitive decline [78, 79]. On the contrary, it has the drawback that it does not contemplate the menopause transition period because the hormonal change is very sudden, and the loss of the ovaries reduces the production of hormones such as testosterone. Nevertheless, as mentioned before, hypoestrogenism induced by ovariectomy shares the main characteristics of human menopause, such as a similar hormonal profile, HPG axis dysregulation, as well as cognitive and cardiometabolic alterations that are present in menopausal women that maintain their reproductive system intact [78, 79].

Among the different models of metabolic syndrome [61, 63, 68], and in humans [88], high-caloric diets, sedentarism, and obesity are independently associated with MS, in contrast to hypoestrogenism (ovariectomy model) that per se generates metabolic syndrome (this proposal). However, due to the wide use of ovariectomy in combination with hypercaloric diets to develop metabolic disorders, most authors have dismissed the results offered by ovariectomy itself; given more importance to the combination with hypercaloric diets for MS development [89–94]. However, hypoestrogenism-induced MS could yield interesting and necessary data in understanding metabolic complications originated by menopause, because estrogens play a crucial role in regulating metabolic-energetics, while their loss leave the body "unprotected" favoring the development of MS independently of the diet used. Accordingly, the success of hypoestrogenism induced by ovariectomy as a MS model could depend on several factors that need a deeper evaluation, like (1) rodent species: Wistar and Sprague–Dawley rats present the greatest development of MS factors, (2) age of the animals at the time of surgery: pre-puber, young, adult or old; an adult age is the best to perform the surgery and achieve the successful establishment of MS, (3) time in which the animals are in hypoestrogenic state: after 12 weeks the main factors associated with MS do appear (Table 1). Therefore, a combination

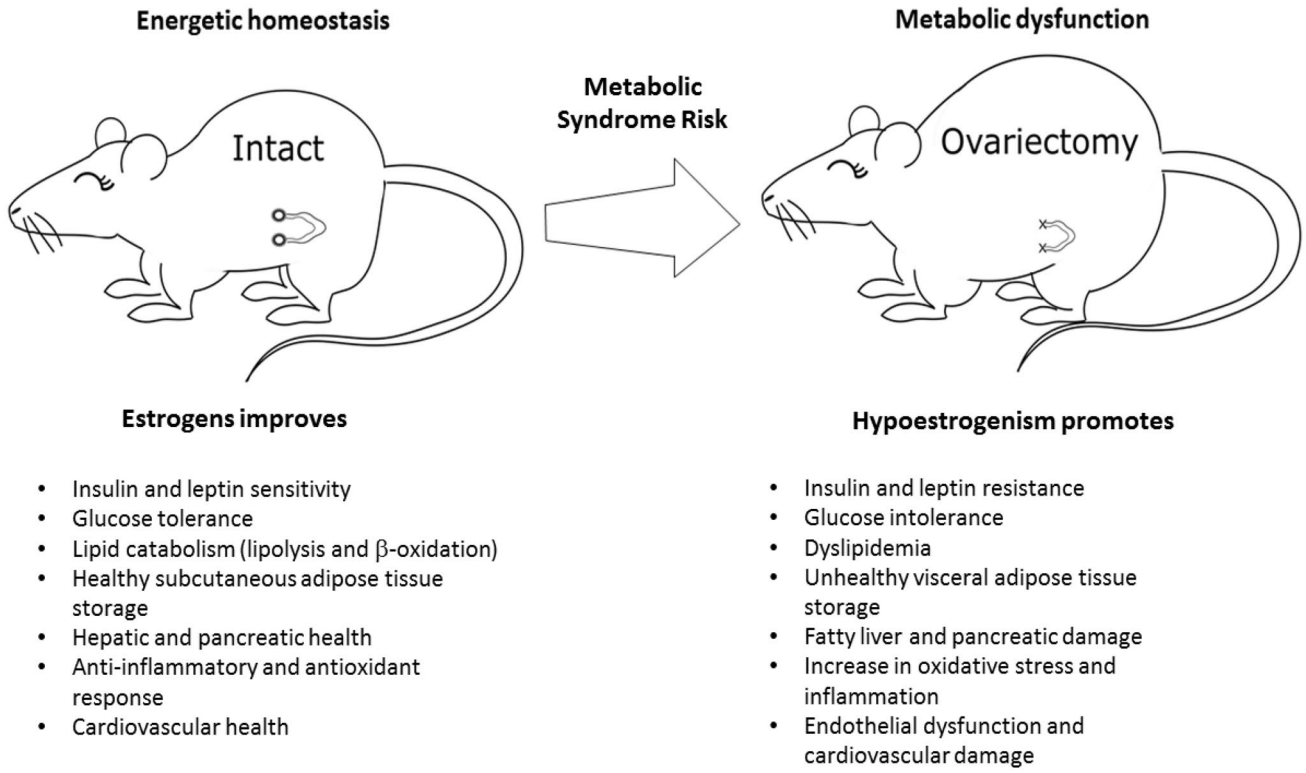

Fig. 3 Ovariectomized rodents as a menopausal metabolic syndrome model. Estrogenic deficit promotes the development of main risk factors of metabolic syndrome

of all these variables could allow the effective achievement of a MS model.

Conclusion

As mentioned, MS-induced by hypercaloric diets can promote the display of multiple pathologies [62, 63]; in this sense, it should be noticed that ovariectomy-induced MS favors the manifestation of pathologies similar to those with hypercaloric diets or a combination of both; for example, cardiomyopathy, hepatic steatosis, kidney damage, inflammatory state and hypertension [65, 70, 71, 81, 83, 95–98], which also have been described in menopause, and that could be a consequence from a predominant hypoestrogenic state [29, 99–101]. Taken together, we suggest that ovariectomy per se can be used as a "menopausal metabolic syndrome model", mainly because the physiopathology of MS that develops in menopause could be different to the one with radical changes in diet; even the main features of menopausal metabolic syndrome could be compared with other MS models. In this way, a more accurate approximation should be made to the development of MS in postmenopausal women, which might imply the search for more specific treatments for this population.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Arnold AP (2010) Promoting the understanding of sex differences to enhance equity and excellence in biomedical science. Biol Sex Differ 1(1):1–3
2. Morrow EH (2015) The evolution of sex differences in disease. Biol Sex Differ 6(5):1–7
3. Clayton JA, Collins FS (2014) Policy: NIH to balance sex in cell and animal studies. Nature 509(7500):282–283
4. Gilbert LI, Bollenbacher WE, Granger NA (1980) Insect endocrinology: regulation of endocrine glands, hormone titer, and hormone metabolism. Annu Rev Physiol 42(1):493–510
5. Davies JP (1995) Plant hormones: physiology, biochemistry and molecular biology. Kluwer Academic Publishers 1–12

6. Köhrle J (2018) Thyroid Hormones and Derivatives: Endogenous Thyroid Hormones and Their Targets. Methods Mol Biol 1801:85–104
7. De Groef B, Grommen SVH, Darras VM (2018) Forever young: endocrinology of paedomorphosis in the Mexican axolotl (Ambystoma mexicanum). Gen Comp Endocrinol 266:194–201
8. Arnold AP (2017) A general theory of sexual differentiation. J Neurosci Res 95(1–2):291–300
9. Dos Santos AC, Viana DC, de Oliveira GB, Lobo LM, Assis-Neto AC (2015) Intrauterine sexual differentiation: biosyntesis and action of sexual steroid hormones. Braz Arch Biol Technol 58(3):395–405
10. Palmer BF, Clegg DJ (2015) The sexual dimorphism of obesity. Mol Cell Endocrinol 402C:113–119
11. Mauvais-Jarvis F, Clegg DJ, Hevener AL (2013) The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev 34(3):309–338
12. Lizcano F, Guzmán G (2014) Estrogen deficiency and the origin of obesity during menopause. Biomed Res Int 2014:1–11
13. Palmisano BT, Zhu L, Stafford JM (2017) Role of estrogens in the regulation of liver lipid metabolism. Adv Exp Med Biol 1043:227–256
14. Chen JQ, Brown TR, Russo J (2009) Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. Biochim Biophys Acta 1793(7):1128–1143
15. Mauvais-Jarvis F, Clegg DJ, Hevener AL (2011) The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev 34(3):309–338
16. Xu Y, López M (2018) Central regulation of energy metabolism by estrogens. Mol Metab 15:104–115
17. Trenti A, Tedesco S, Boscaro C, Trevisi L, Bolego C, Cignarella A (2018) Estrogen, angiogenesis, immunity and cell metabolism: solving the puzzle. Int J Mol Sci 19(3):859
18. Chakrabarti S, Lekontseva O, Davidge ST (2008) Estrogen is a modulator of vascular inflammation. Int Union of Biochem and Mol Biol Life 60(6):376–382
19. Strehlow K, Rotter S, Wassmann S, Adam O, Grohé C, Laufs K, Böhm M, Nickenig G (2003) Modulation of antioxidant enzyme expression and function by estrogen. Circ Res 93(2):170–177
20. Sheng-Huang C, Chieh-Hsin C, Mu-Chun Y, Wen-Tung H, Chia-Ying H, Ya-Ting H, Wan-Ling SU, Jiuan-Jen S, Chih-Yang H, Jer-Yuh L (2015) Effects of estrogen on glutathione and catalase levels in human erythrocyte during menstrual cycle. Biomedical reports 3(2):266–268
21. Straub RH (2007) The complex role of estrogens in inflammation. Endocr Rev 28(5):521–574
22. Gupta S, Villalón CM, Mehrotra S, de Vries R, Garrelds IM, Saxena PR, MaassenVanDenBrink A (2007) Female sex hormones and rat dural vasodilatation to CGRP, periarterial electrical stimulation and capsaicin. Headache: J Head Face Pain 47(2):225–235
23. González-Hernández A, Marichal-Cancino BA, Lozano-Cuenca J, López-Canales JS, Muñoz-Islas E, Ramírez-Rosas MB, Villalón CM (2016) Heteroreceptors modulating CGRP release at neurovascular junction: potential therapeutic implications on some vascular-related diseases. Biomed Res Int 2016:2056786
24. Knowlton AA, Lee AR (2012) Estrogen and the cardiovascular system. Pharmacol Ther 135(1):54–70
25. Wallace IR, McKinley MC, Bell PM, Hunter SJ (2013) Sex hormone binding globulin and insulin resistance. Clin Endocrinol (Oxf) 78(3):321–329
26. Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Rees M, Santoro N, Simoncini T (2015) Menopause. Nat Rev Dis Primers 1:15004
27. Gourdy P, Guillaume M, Fontaine C, Adlanmerini M, Montagner A, Laurell H, Lenfant F, Arnal JF (2018) Estrogen receptor subcellular localization and cardiometabolism. Mol Metab 15:56–69
28. Ahem M, Yeah A (2010) Gender differences in coronary heart disease. Neth Heart J 18(12):598–602
29. Carr MC (2003) The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 88(6):2404–2411
30. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation. Int Circ 120(16):1640–1645
31. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P (2008) Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 28(6):1039–1049
32. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C (2004) Definition of metabolic syndrome: report of the national heart, lung, and blood institute/american heart association conference on scientific issues related to definition. Circulation 109(3):433–438
33. Murguía-Romero M, Jiménez-Flores JR, Sigrist-Flores SC, Espinoza-Camacho MA, Jiménez-Morales M, Piña E, Méndez-Cruz AR, Villalobos-Molina R, Reaven GM (2013) Plasma triglyceride/HDL- cholesterol ratio, insulin resistance, and cardiometabolic risk in young adults. J Lipid Res 54(10):2795–2799
34. Hopps E, Noto D, Caimi G, Averna MR (2010) A novel component of the metabolic syndrome: the oxidative stress. Nutr Metab Cardiovasc Dis 20(1):72–77
35. Torres S, Fabersani E, Marquez A, Gauffin-Cano P (2018) Adipose tissue inflammation and metabolic syndrome. The proactive role of probiotics. Eur J Nutr 58(1):27–43
36. Stefanska A, Bergmann K, Sypniewska G (2015) Metabolic syndrome and menopause: pathophysiology, clinical and diagnostic significance. Adv Clin Chem 72:1–75
37. Ziaei S, Mohseni H (2013) Correlation between hormonal statuses and metabolic syndrome in postmenopausal women. J Family Reprod Health 7(2):63–66
38. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K (2008) Menopause and the metabolic syndrome: the study of women's health across the nation. Arch Intern Med 168(14):1568–1575
39. Cho GJ, Lee JH, Park HT, Shin JH, Hong SC, Kim T, Hur JY, Lee KW, Park YK, Kim SH (2008) Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause 15(3):524–529
40. De Marchi R, Dell'Agnolo CM, Lopes TCR, Gravena AAF, Demitto MO, Brischiliari SCR, Borghesan DHP, Carvalho MDB, Pelloso SM (2017) Prevalence of metabolic syndrome in pre- and postmenopausal women. Arch Endocrinol Metab 61(2):160–166
41. Kim HM, Park J, Ryu SY, Kim J (2007) The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 30(3):701–706
42. Ruan X, Jin J, Hua L, Liu Y, Wang J, Liu S (2010) The prevalence of metabolic syndrome in Chinese postmenopausal women and the optimum body composition indices to predict it. Menopause 17(3):566–570
43. Eshtiaghi R, Esteghamati A, Nakhjavani M (2010) Menopause is an independent predictor of metabolic syndrome in Iranian women. Maturitas 65(3):262–266
44. Kunicki M, Rudnicka E, Skórska J, Calik-Ksepka AI, Smolarczyk R (2018) Insulin resistance indexes in women with premature ovarian insufficiency - a pilot study. Ginekol Pol 89(7):364–369

45. Sowers M, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, Yosef M, Symons J (2007) Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 92(3):895–901
46. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR (2008) Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 32(6):949–958
47. Fonseca-Alaniz MH, Takada J, Alonso-Vale MI, Lima FB (2007) Adipose tissue as an endocrine organ: from theory to practice. J Pediatr (Rio J) 83(5):192–203
48. da Cruz Fonseca EJN, Oliveira Rocha TP, Lustosa Nogueira LA, Braga de Melo J, Lima e Silva B, Jardim Lopes E, Batalha Serra C, Gomes Andrade MV, Bandeira de Sous SM, de Figueredo Neto JA (2018) Metabolic syndrome and insulin resistance by HOMA-IR in menopause. Int J Cardiovasc Sci 31(3):201–208
49. Farahmand M, Ramezani Tehrani F, Simbar M, Mehrabi Y, Khalili D, Azizi F (2014) Does metabolic syndrome or its components differ in naturally and surgically menopausal women? Climacteric 17(4):348–355
50. Lobo RA (2007) Surgical menopause and cardiovascular risks. Menopause 14(3 Pt 2):562–566
51. Dørum A, Tonstad S, Liavaag AH, Michelsen TM, Hildrum B, Dahl AA (2008) Bilateral oophorectomy before 50 years of age is significantly associated with the metabolic syndrome and Framingham risk score: a controlled, population-based study (HUNT-2). Gynecol Oncol 109(3):377–383
52. Di Carlo C, Di Spiezio SA, Bifulco G, Tommaselli GA, Guerra G, Rippa E, Mandato VD, Nappi C (2007) Postmenopausal hypoestrogenism increases vasoconstrictor neuropeptides and decreases vasodilator neuropeptides content in arterial-wall autonomic terminations. Fertil Steril 88(1):95–99
53. Ebtekar F, Dalvand S, Ghanei R (2018) The prevalence of metabolic syndrome in postmenopausal women: a systematic review and meta-analysis in Iran. Diabetes Metab Syndr: Clin Res Rev 12(6):955–960
54. Howard BV, Kuller L, Langer R, Manson JE, Allen C, Assaf A, Cochrane BB, Larson JC, Lasser N, Rainford M, Van Horn L, Stefanick ML, Trevisan M (2005) Women's health initiative. Risk of cardiovascular disease by hysterectomy status, with and without oophorectomy: the women's health initiative observational study. Circulation 111(12):1462–1470
55. Mesch VR, Siseles NO, Maidana PN, Boero LE, Sayegh F, Prada M, Royer M, Schreier L, Benencia HJ, Berg GA (2008) Androgens in relationship to cardiovascular risk factors in the menopausal transition. Climacteric 11(6):509–517
56. Chedraui P, Hidalgo L, Chavez D, Morocho N, Alvarado M, Huc A (2007) Menopausal symptoms and associated risk factors among postmenopausal women screened for the metabolic syndrome. Arch Gynecol Obstet 275(3):161–168
57. Lumeng CN, Saltiel AR (2011) Inflammatory links between obesity and metabolic disease. J Clin Invest 121(6):2111–2117
58. Emanuela F, Grazia M, de Marco R, Maria Paola L, Giorgio F, Marco B (2012) Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab 2012:476380
59. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 105(2):141–150
60. Chen L, Chen R, Wang H, Liang F (2015) Mechanisms linking inflammation to insulin resistance. Int J Endocrinol 2015:508409
61. Rodríguez-Correa E, González-Pérez I, Clavel-Pérez PI, Contreras-Vargas Y, Carvajal K (2020) Biochemical and nutritional overview of diet-induced metabolic syndrome models in rats: what is the best choice? Nutr Diabetes 10:24
62. Lehnen AM, Rodrigues B, Irigoyen MC, De Angelis K, Schaan BD (2013) Cardiovascular changes in animal models of metabolic syndrome. J Diabetes Res 2013:761314
63. Wong SK, Chin KY, Suhaimi FH, Fairus A, Ima-Nirwana S (2016) Animal models of metabolic syndrome: a review. Nutr Metab (Lond) 13:65
64. Balderas-Villalobos J, Molina-Muñoz T, Mailloux-Salinas P, Bravo G, Carvajal K, Gómez-Viquez NL (2013) Oxidative stress in cardiomyocytes contributes to decreased SERCA2a activity in rats with metabolic syndrome. Am J Physiol Heart Circ Physiol 305(9):1344–1353
65. Zhang R, Su D, Zhu W, Huang Q, Liu M, Xue Y, Zhang Y, li D, Zhao A, Liu Y (2014) Estrogen suppresses adipogenesis by inhibiting S100A16 expression. J Mol Endocrinol 52(3):235–244
66. Niu L, Han DW, Xu RL, Han B, Zhou X, Wu HW, Li SH, Qu CX, Liu M (2016) A high-sugar high-fat diet induced metabolic syndrome shows some symptoms of alzheimer's disease in rats. J Nutr Health Aging 20(5):509–513
67. Pérez-Torres I, Roque P, El Hafidi M, Diaz-Diaz E, Baños G (2009) Association of renal damage and oxidative stress in a rat model of metabolic syndrome. Influ Gender Free Radic Res 43(8):761–771
68. Carvajal K, El Hafidi M, Marin-Hernández A, Moreno-Sánchez R (2005) Structural and functional changes in heart mitochondria from sucrose-fed hypertriglyceridemic rats. Biochim Biophys Acta 1709(3):231–239
69. Yamaguchi Y, Yoshikawa N, Kagota S, Nakamura K, Haginaka J, Kunitomo M (2006) Elevated circulating levels of markers of oxidative-nitrative stress and inflammation in a genetic rat model of metabolic syndrome. Nitric Oxide 15(4):380–386
70. Tawfik SH, Mahmoud BF, Saad MI, Shehata M, Kamel MA, Helmy MH (2015) Similar and additive effects of ovariectomy and diabetes on insulin resistance and lipid metabolism. Biochem Res Int 2015:567945
71. Fahmy MK, Sayyed HG, Elrahim EAA, Farag RTA (2018) Superimposed effect of ovariectomy on type 2 diabetes mellitus in Wistar rats. Alex J Med 54:129–137
72. Saengsirisuwan V, Pongseeda S, Prasannarong M, Vichaiwong K, Toskulkao C (2009) Modulation of insulin resistance in ovariectomized rats by endurance exercise training and estrogen replacement. Metabolism 58(1):38–47
73. Misso ML, Hewitt KN, Boon WC, Murata Y, Jones ME, Simpson ER (2005) Cholesterol feeding prevents adiposity in the obese female aromatase knockout (ArKO) mouse. Horm Metab Res 37(1):26–31
74. Bader MI, Wober J, Kretzschmar G, Zierau O, Vollmer G (2011) Comparative assessment of estrogenic responses with relevance to the metabolic syndrome and to menopausal symptoms in wild-type and aromatase-knockout mice. J Steroid Biochem Mol Biol 127(3–5):428–434
75. Choi EK, Kim WK, Sul OJ, Park YK, Kim ES, Suh JH, Yu R, Choi HS (2013) TNFRSF14 deficiency protects against ovariectomy-induced adipose tissue inflammation. J Endocrinol 220(1):25–33
76. Ribas V, Nguyen MT, Henstridge DC, Nguyen AK, Beaven SW, Watt MJ, Hevener AL (2010) Impaired oxidative metabolism and inflammation are associated with insulin resistance in ERalpha-deficient mice. Am J Physiol Endocrinol Metab 298(2):E304–E319
77. Zhu L, Martinez MN, Emfinger CH, Palmisano BT, Stafford JM (2014) Estrogen signaling prevents diet-induced hepatic insulin resistance in male mice with obesity. Am J Physiol Endocrinol Metab 306(10):E1188–E1197
78. Diaz Brinton R (2012) Minireview: translational animal models of human menopause: challenges and emerging opportunities. Endocrinology 153(8):3571–3578

79. Koebele SV, Bimonte-Nelson HA (2016) Modeling menopause: the utility of rodents in translational behavioral endocrinology research. Maturitas 87:5–17
80. Majumdar AS, Giri PR, Pai SA (2014) Resveratrol- and melatonin-abated ovariectomy and fructose diet-induced obesity and metabolic alterations in female rats. Menopause 21(8):876–885
81. Sivasinprasasn S, Sa-Nguanmoo P, Pratchayasakul W, Kumfu S, Chattipakorn SC, Chattipakorn N (2015) Obese-insulin resistance accelerates and aggravates cardiometabolic disorders and cardiac mitochondrial dysfunction in estrogen-deprived female rats. Age (Dordr) 37(2):28
82. Zhang L, Zhou M, Fang G, Tang Y, Chen Z, Liu X (2013) Hypocholesterolemic effect of capsaicinoids by increased bile acids excretion in ovariectomized rats. Mol Nutr Food Res 57:1080–1088
83. Bendale DS, Karpe PA, Chhabra R, Shete SP, Shah H, Tikoo K (2013) 17-β Oestradiol prevents cardiovascular dysfunction in post-menopausal metabolic syndrome by affecting SIRT1/AMPK/H3 acetylation. Br J Pharmacol 170(4):779–795
84. Hassan HA, Abdel-Wahhab MA (2012) Effect of soybean oil on atherogenic metabolic risks associated with estrogen deficiency in ovariectomized rats: dietary soybean oil modulate atherogenic risks in ovariectomized rats. J Physiol Biochem 68(2):247–253
85. Zhen PP, Duan JH, Zhao Q et al (2011) Phytoestrogen α-zearalanol improves vascular function in ovariectomized hyperhomocysteinemic rats. Atherosclerosis 215(2):309–315
86. Koyuncu FM, Ozbilgin K, Kuscu NK, Inan S, Vatansever S, Ceylan E (2006) The effect of oestradiol and neta on immunohistochemical staining of iNOS and eNOS in coronary arteries of ovariectomized rats. Histol Histopathol 21(4):367–371
87. Mohamed MT, Abuelezz SA, Atalla SS, El Aziz LFA, Gorge SS (2017) The anti-osteoporotic and anti-atherogenic effects of alendronate and simvastatin in ovariectomized rats fed high fat diet: a comparative study of combination therapy versus monotherapy. Biomed Pharmacothe 89:1115–1124
88. Wagner A, Dallongeville J, Haas B, Ruidavets JB, Amouyel P, Ferrières J, Simon C, Arveiler D (2012) Sedentary behaviour, physical activity and dietary patterns are independently associated with the metabolic síndrome. Diabetes Metabolism 38:428–435
89. Lee YL, Lin KL, Wu BN, Chuang SM, Wu WJ, Lee YC, Ho WT, Juan YS (2018) Epigallocatechin-3-gallate alleviates bladder overactivity in a rat model with metabolic syndrome and ovarian hormone deficiency through mitochondria apoptosis pathways. Sci Rep 8(1):5358
90. Medina-Contreras JML, Colado-Velázquez J 3rd, Gómez-Viquez NL, Mailloux-Salinas P, Pérez-Torres I, Aranda-Fraustro A, Carvajal K, Bravo G (2017) Effects of topical capsaicin combined with moderate exercise on insulin resistance, body weight and oxidative stress in hypoestrogenic obese rats. Int J Obes (Lond) 41(5):750–758
91. Kawvised S, Wattanathorn J, Thukham-Mee W (2017) Neuroprotective and cognitive-enhancing effects of microencapsulation of mulberry fruit extract in animal model of menopausal women with metabolic syndrome. Oxid Med Cell Longev 2017:2962316
92. Guerra RC, Zuñiga-Muñoz A, Guarner Lans V, Díaz-Díaz E, Tena Betancourt CA, Pérez-Torres I (2014) Modulation of the activities of catalase, cu-zn, mn superoxide dismutase, and glutathione peroxidase in adipocyte from ovariectomised female rats with metabolic syndrome. Int J Endocrinol 2014:175080
93. Tan Z, Zhou LJ, Mu PW, Liu SP, Chen SJ, Fu XD, Wang TH (2012) Caveolin-3 is involved in the protection of resveratrol against high-fat-diet-induced insulin resistance by promoting GLUT4 translocation to the plasma membrane in skeletal muscle of ovariectomized rats. J Nutr Biochem 23(12):1716–1724
94. Hamilton DJ, Minze LJ, Kumar T, Cao TN, Lyon CJ, Geiger PC, Hsueh WA, Gupte AA (2016) Estrogen receptor alpha activation enhances mitochondrial function and systemic metabolism in high-fat-fed ovariectomized mice. Physiol Rep 4(17):e12913
95. Prasannarong M, Vichaiwong K, Saengsirisuwan V (2012) Calorie restriction prevents the development of insulin resistance and impaired insulin signaling in skeletal muscle of ovariectomized rats. Biochim Biophys Acta 1822(6):1051–1061
96. Panneerselvam S, Packirisamy RM, Bobby Z, Elizabeth Jacob S, Sridhar MG (2016) Soy isoflavones (Glycine max) ameliorate hypertriglyceridemia and hepatic steatosis in high fat-fed ovariectomized Wistar rats (an experimental model of postmenopausal obesity). J Nutr Biochem 38:57–69
97. Pósa A, Szabó R, Kupai K, Csonka A, Szalai Z, Veszelka M, Török S, Daruka L, Varga C (2015) Exercise training and calorie restriction influence the metabolic parameters in ovariectomized female rats. Oxid Med Cell Longev 2015:787063
98. Morra EA, Rodrigues PL, Jesus ICG, Do Val Lima PR, Ávila RA, Zanardo TÉC, Nogueira BV, Bers DM, Guatimosim S, Stefanon I, Ribeiro Júnior RF (2018) Endurance training restores spatially distinct cardiac mitochondrial function and myocardial contractility in ovariectomized rats. Free Radic Biol Med 130:174–188
99. Newson L (2018) Menopause and cardiovascular disease. Post Reprod Health 24(1):44–49
100. Ahmed SB (2007) Menopause and chronic kidney disease. Semin Nephrol 37(4):404–411
101. Völzke H, Schwarz S, Baumeister SE, Wallaschofski H, Schwahn C, Grabe HJ, Kohlmann T, John U, Dören M (2007) Menopausal status and hepatic steatosis in a general female population. Gut 56(4):594–595
102. Babaei P, Mehdizadeh R, Ansar MM, Damirchi A (2010) Effects of ovariectomy and estrogen replacement therapy on visceral adipose tissue and serum adiponectin levels in rats. Menopause Int 16(3):100–104
103. Munhos Hermoso DA, Shimada LB, Gilglioni EH, Constantin J, Mito MS, Hermoso AP, Salgueiro-Pagadigorria CL, Iwamoto EL (2016) Melatonin protects female rats against steatosis and liver oxidative stress induced by oestrogen deficiency. Life Sci 157:178–186
104. Busserolles J, Mazur A, Gueux E, Rock E, Rayssiguier Y (2002) Metabolic syndrome in the rat: females are protected against the prooxidant effect of highsucrose diet. Exp Biol Med 227(9):837–842
105. Bitto A, Burnett BP, Polito F, Marini H, Levy RM, Armbruster MA, Minutoli L, Di Stefano V, Irrera N, Antoci S, Granese R, Squadrito F, Altavilla D (2008) Effects of genistein aglycone in osteoporotic, ovariectomized rats: a comparison with alendronate, raloxifene and oestradiol. Br J Pharmacol 155(6):896–905
106. Xu J, Xiang Q, Lin G, Fu X, Zhou K, Jiang P, Zheng S, Wang T (2012) Estrogen improved metabolic syndrome through downregulation of VEGF and HIF-1α to inhibit hypoxia of periaortic and intra-abdominal fat in ovariectomized female rats. Mol Biol Rep 39(8):8177–8185
107. Rattanavichit Y, Chukijrungroat N, Saengsirisuwan V (2016) Sex differences in the metabolic dysfunction and insulin resistance of skeletal muscle glucose transport following high fructose ingestion. Am J Physiol Regul Integr Comp Physiol 311(6):1200–1212
108. Gorres BK, Bomhoff GL, Gupte AA, Geiger PC (2011) Altered estrogen receptor expression in skeletal muscle and adipose tissue of female rats fed a high-fat diet. J Appl Physiol 110(4):1046–1053
109. Park YM, Rector RS, Thyfault JP, Zidon TM, Padilla J, Welly RJ, Meers GM, Morris ME, Britton SL, Koch LG, Booth FW, Kanaley JA, Vieira-Potter VJ (2016) Effects of ovariectomy and

intrinsic aerobic capacity on tissue-specific insulin sensitivity. Am J Physiol Endocrinol Metab 310(3):E190–E199
110. Rogers NH, Perfield JW 2nd, Strissel KJ, Obin MS, Greenberg AS (2009) Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. Endocrinology 150(5):2161–2168
111. Valencia AP, Schappal AE, Morris EM, Thyfault JP, Lowe DA, Spangenburg EE (2016) The presence of the ovary prevents hepatic mitochondrial oxidative stress in young and aged female mice through glutathione peroxidase. Exp Gerontol 73:14–22
112. Choi EK, Rajasekaran M, Sul OJ, Joe Y, Chung HT, Yu R, Choi HS (2018) Impaired insulin signaling upon loss of ovarian function is associated with a reduction of tristetraprolin and an increased stabilization of chemokine in adipose tissue. Mol Cell Endocrinol 461:122–131
113. Ben-Shmuel S, Scheinman EJ, Rashed R, Orr ZS, Gallagher EJ, LeRoith D, Rostoker R (2015) Ovariectomy is associated with metabolic impairments and enhanced mammary tumor growth in MKR mice. J Endocrinol 227(3):143–151
114. Tominaga K, Yamauchi A, Egawa T, Tanaka R, Kawahara S, Shuto H, Kataoka Y (2011) Vascular dysfunction and impaired insulin signaling in high-fat diet fed ovariectomized mice. Microvasc Res 82(2):171–176
115. Dalmasso C, Maranon R, Patil C, Bui E, Moulana M, Zhang H, Smith A, Yanes Cardozo LL, Reckelhoff JF (2016) Cardiometabolic effects of chronic hyperandrogenemia in a new model of postmenopausal polycystic ovary syndrome. Endocrinology 157(7):2920–2927
116. Maliqueo M, Sun M, Johansson J, Benrick A, Labrie F, Svensson H, Lönn M, Duleba AJ, Stener-Victorin E (2013) Continuous administration of a P450 aromatase inhibitor induces polycystic ovary syndrome with a metabolic and endocrine phenotype in female rats at adult age. Endocrinology 154(1):434–445
117. Romero-Aleshire MJ, Diamond-Stanic MK, Hasty AH, Hoyer PB, Brooks HL (2009) Loss of ovarian function in the VCD mouse-model of menopause leads to insulin resistance and a rapid progression into the metabolic syndrome. Am J Physiol Regul Integr Comp Physiol 297(3):R587–R592
118. Borbélyová V, Domonkos E, Bábíčková J, Tóthová Ľ, Kačmárová M, Uličná O, Ostatníková D, Hodosy J, Celec P (2017) Does long-term androgen deficiency lead to metabolic syndrome in middle-aged rats? Exp Gerontol 98:38–46
119. Iwasa T, Matsuzaki T, Yano K, Yiliyasi M, Kuwahara A, Matsui S, Irahara M (2018) Effects of chronic testosterone administration on the degree of preference for a high-fat diet and body weight in gonadal-intact and ovariectomized female rats. Behav Brain Res 349:102–108