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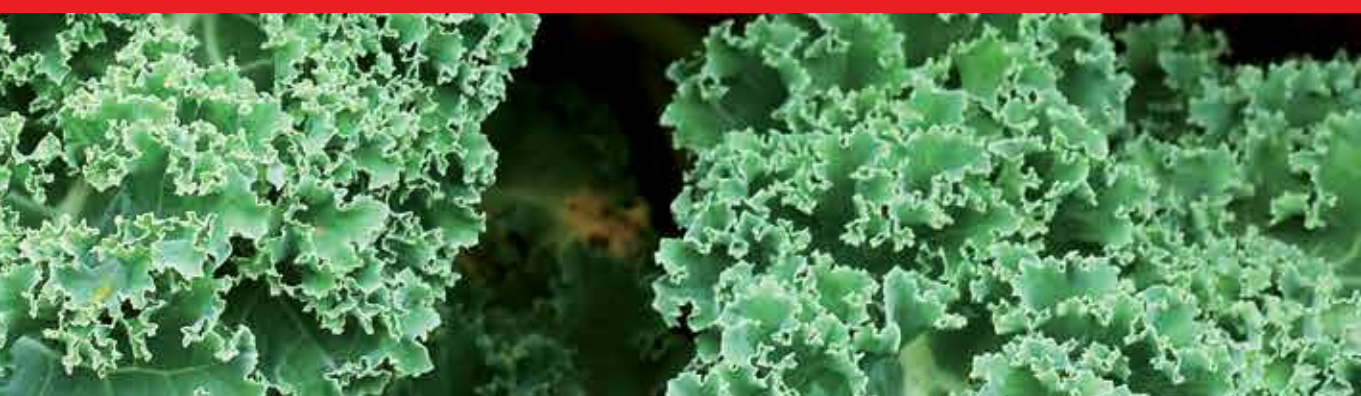
A Multidisciplinary Look at Menopause

Edited by Juan Francisco Rodriguez-Landa and Jonathan Cueto-Escobedo



A MULTIDISCIPLINARY LOOK AT MENOPAUSE

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and **Jonathan Cueto-Escobedo**

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http://dx.doi.org/10.5772/66558
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Notice

First published in Croatia, 2017 by INTECH d.o.o.
eBook (PDF) Published by IN TECH d.o.o.
Place and year of publication of eBook (PDF): Rijeka, 2019.
IntechOpen is the global imprint of IN TECH d.o.o.
Printed in Croatia

Legal deposit, Croatia: National and University Library in Zagreb

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p. cm.

Print ISBN 978-953-51-3405-3

Online ISBN 978-953-51-3406-0

eBook (PDF) ISBN 978-953-51-4708-4

Meet the editors

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Contents

Preface

Around the world, women in their fifties would experience menopause. To detail the impact of this phenomenon, it is important to highlight that about 60% of these women will experience sleep disorders, sexual dysfunctions, anxiety, and depressive disorders, in addition to muscle or joint pain, among others, independently of ethnic origin or sociodemographic factors. These symptoms impact directly in the quality of life, produce a loss of productivity, and incur increased healthcare utilization. The impact is such that menopause must be considered in labor environment since it can trigger issues as poor concentration, tiredness, poor memory, depressed feelings, and lowered confidence. It is noteworthy that most women feel unwilling to disclose menopause-related health issues to line managers (most men or younger women). Research on this area suggests that greater awareness and support of managers about menopause, flexible working hours, control over workplace temperature and ventilation, and access to cold drinking water and toilets are effective in improving wellness and productivity in menopausal women. These approaches should not be taken lightly since inclusively the World Health Organization has expressed concerns about the specific necessities of women experiencing menopause. Other approaches comprise the hormonal replacement therapy, healthy habits as exercise and yoga, and nutritional factors as consumption of soy and natural products rich in phytoestrogens. Hormonal replacement therapy has been one of the most widespread approaches to the treatment of menopause-related diseases; however, the interaction of estradiol with estrogen receptors on tumoral tissue is able to trigger proliferative effects that highlight the latent risk of this therapy. Alternative therapies as phytoestrogen-rich diets have shown encouraging results but still need more research since effects are still diverse and not fully understood. Given the complexity of symptoms, multidisciplinary approaches to treatment seem to be necessary. In this sense, multidisciplinary models to evaluate and manage women experiencing menopause include gynecologists, endocrinologists, psychologist, and clinical nurse specialist and have shown benefits on coordination of patient care, education, communication, and evidence-based decision-making. Taken together, the characteristics of menopause compel us to approach the phenomenon with a multidisciplinary point of view that include evolutionary, neurobiological, psychosocial, and cultural factors in order to improve our understanding and management of this phenomenon; it is exactly the purpose of the present book *A Multidisciplinary Look at Menopause*. Thanks to all the contributing authors, we hope you find these efforts satisfactory and wish you a good reading.

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Chapter 1

Introductory Chapter: A Multidisciplinary Look at Menopause

Juan Francisco Rodríguez-Landa and
Jonathan Cueto-Escobedo

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70114

1. Menopause as a natural process

Menopause is a natural and inevitable period of ageing in women that is well known to represent the end of reproductive life through the failure of ovarian function, accompanied by a decrease in estrogen and progestin production in the periphery and brain [1, 2]. Sexual hormones, such as estradiol and progesterone, help regulate metabolic function and interact with a wide range of neurotransmitters, such as serotonin, dopamine, λ-aminobutyric acid, and glutamate, among others [3]. Lower concentrations of these hormones during menopause have been associated with the development of specific diseases. Hormonal changes during menopause are also involved in sex differences in brain disorders that develop in aged individuals. The United States National Institutes of Health established a research priority to encourage investigations of the impact of gender on normal brain function and central nervous system-related diseases [4]. Studying menopause from a multidisciplinary perspective will help unveil different factors that affect health in this specific stage of life in women.

During menopause, lower hormone production is related to a higher incidence of vasomotor symptoms, such as hot flashes, vaginal dryness, osteoporosis, cognitive deterioration, irritability, anxiety, and mood disorders (e.g., depression) [5–8]. Menopause can occur gradually as a natural ageing process, culminating around age 50 years, or it can occur suddenly after surgical procedures, such as oophorectomy, salpingo-oophorectomny, and hysterectomy [9]. When menopause is caused by surgical manipulations, the negative symptoms can be more severe than when it occurs naturally [10]. Changes that occur during menopause interact with genetic, nutritional, sociocultural, and demographic factors [11, 12], differentially impacting quality of life in menopausal women. Research on menopause requires considerations of biology, physiology, sociology, and psychology to achieve better knowledge of this physiological

state in women and design the therapeutic approaches that focus on pharmacological treatment and psychological and physical therapy.

2. A multidisciplinary look at menopause

In this book, Dr. Kirchengast (Chapter 2) approaches menopause as a normal female stage that is a product of the overall ontogenetic and phylogenetic development of *Homo sapiens*, with a focus on evolutionary anthropology. This chapter is complemented by the work of Dr. Rovirosa-Hernández and collaborators (Chapter 3) that details the physiological changes that occur at the end of the reproductive life cycle in nonhuman primates. They compare these changes with those that are observed in menopausal women to gain a better understanding of human menopause.

Dr. Afridi Iqbal (Chapter 4) describes the ways in which psychological factors impact self-concepts and the mental health of women who experience menopause and the ways in which these factors can trigger variations in mood and such disorders as anxiety and depression.

Dr. García-Ríos and collaborators (Chapter 5) discuss the changes in serotonergic neurotransmission associated with changes in the concentrations of steroid hormones in the brain that accompany menopause and are related to greater vulnerability to depression and a lower response to antidepressant therapy in depressed menopausal women. These data are relevant when considering that aged women respond differently to antidepressants compared with young women, which could be related to lower levels of steroid hormones that negatively impact neurotransmitter function. Preclinical studies have shown that antidepressant drug treatment in middle-age ovariectomized rats that have a long-term absence of ovarian hormones is devoid of antidepressant-like effects, but if they are combined with estrogens, then an antidepressant-like effect is detected [13].

Menopause is not considered a disease but rather a natural stage of female development. However, menopause is sometimes associated with several illnesses that are associated with physical, physiological, and psychosocial factors. The most widely used treatment for menopause-related changes is hormone replacement therapy with estrogen, progestin, and their derivatives [14, 15]. Hormone replacement therapy has been shown to reduce such symptoms as bone loss, hot flashes, irritability, and mood swings [16, 17] and improve overall mental health [7]. Nevertheless, hormone replacement therapy also has side effects that restrict its long-term use in some women [18, 19]. Consequently, medicinal alternatives are needed to ameliorate menopause symptoms with a lower risk of severe side effects. Therapeutic alternatives mainly consist of dietary supplements that contain natural compounds, such as phytoestrogens, including isoflavones, flavones, lignans, coumestans, and stilbenes. Preclinical studies have shown that the phytoestrogen genistein reverses anxiety-like behavior in an experimental model of surgical menopause [20] and depression-like behavior [21].

Dr. Estrada-Camarena and collaborators (Chapter 6) describe in detail the effects of nonsteroid hormone therapy that is based on the use of natural and synthetic phytoestrogens. They

present preclinical and clinical evidence of the ways in which phytoestrogens interact with specific receptors in the brain to reduce anxiety and depression symptoms and ameliorate other illnesses that are associated with menopause.

Dr. Bittar Simoni (Chapter 7) describes the positive effects of physical activity on health in menopausal women. In his chapter, he discusses the ways in which different exercise regimens can improve body composition, functional performance, strength, and balance, thus positively impacting physical health and emotional and affective states. For example, a positive interaction has been found between estradiol concentrations and physical activity that attenuates endocrine responses to stress [22], thus decreasing irritability, anxiety, and depression symptoms.

3. Concluding remarks

Menopause is characterized by physiological, biological, and psychosocial changes that impact lifestyle and predispose them to the development of different diseases. The current therapeutic approaches are diverse, including drugs, hormones, chemical products of natural origin, meditation, and exercise, each of which have specific risks and benefits. Unfortunately, because of the complexity of the physiological and psychological changes that are associated with menopause, no completely safe and effective treatment for all symptoms has been developed.

Genetic differences can also influence the severity of symptoms and response to conventional therapies [11, 23], thus complicating the development of a general therapeutic approach for all menopausal woman. Understanding the causes of diseases that are associated with menopause and responses to different treatments should utilize a multidisciplinary approach to achieve combined therapeutic strategies for specific groups of menopausal women. Decisions regarding the treatment for menopausal women should consider symptomatology, health status, immediate and long-term health risk, personal life expectations, and the availability and cost of therapy [2]. Safer and more effective therapeutic alternatives for the management of menopausal symptoms need to be developed, specifically for women who present contraindications to hormone therapy. Although great advances have been made from psychological, physiological, pharmacological, and environmental perspectives, still much work needs to be done.

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References

[1] Nelson HD. Menopause. The Lancet. 2008; **371**(9614):760-770

[2] Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Ress M, Santoro N, Simoncini T. Menopause. Nature Reviews. Disease Primers. 2015;**1**:15004

[3] Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Frontiers in Neuroscience. 2015;**9**:37

[4] National Institute of Mental Health. Sex Differences in Brain, Behavior, Mental Health and Mental Disorders. Bethesda, MD, USA: Workshop; 2011. http://www.nimh.nih.gov/research-priorities/scientific-meetings/2011/sex-differences-in-brain-behavior-mental-health-and-mental-disorders/index.shtml [Accessed: May 2, 2017]

[5] Maki PM. Menopause and cognition. In: Lobo RA, editor. Treatment of the Postmenopausal Woman: Basic and Clinical Aspects. Burlington: Academic Press; 2007. pp. 279-285

[6] Alexander IM, Moore A. Treating vasomotor symptoms of menopause: The nurse practitioner's perspective. Journal of the American Academy of Nurse Practitioners. 2007;**19**(3):152-163

[7] Rodríguez-Landa JF, Puga-Olguín A, Germán-Ponciano LJ, García-Ríos RI, Soria-Fregozo C. Anxiety in natural and surgical menopause: Physiologic and therapeutic bases. In: Durbano F, editor. A Fresh Look Anxiety Disorders. Rijeka: InTech; 2015. pp. 173-198

[8] Rosano GM, Spoletini I, Vitale C. Cardiovascular disease in women, is it different to men? The role of sex hormones. Climateric. 2017;**20**(2):125-128

[9] Erekson EA, Martin DK, Ratner ES. Oophorectomy: The debate between ovarian conservation and elective oophorectomy. Menopause. 2013;**20**(1):110-114

[10] Tucker PE, Bulsara MK, Salfinger SG, Tan JJ, Green H, Cohen PA. The effects of preoperative menopausal status and hormone replacement therapy (HRT) on sexuality and quality of life after risk-reducing salpingo-oophorectomy. Maturitas. 2016;**85**:42-48

[11] Hunter MS. Predictors of menopausal symptoms: Psychosocial aspects. Bailliere's Clinical Endocrinology and Metabolism. 1993;**7**(1):33-45

[12] Melby MK, Anderson D, Sievert LL, Obermeyer CM. Methods used in cross-cultural comparisons of vasomotor symptoms and their determinants. Maturitas. 2011;**70**(2):110-119

[13] Vega-Rivera NM, Gallardo-Tenorio A, Fernández-Guasti A, Estrada-Camarena E. The post-ovariectomy interval affects the antidepressant-like action of citalopram combined with ethynyl-estradiol in the forced swim test in middle aged rats. Pharmaceuticals. 2016;**9**:E21

[14] Rapkin AJ, Winer SA. Drospirenone: A novel progestin. Expert Opinion on Pharmacotherapy. 2007;**8**:989-999

[15] Langer RD. The evidence base for HRT: What can we believe? Climateric. 2017;**20**(2):91-96

[16] Freedman MA. Quality of life and menopause: The role of estrogen. Journal of Womens Health. 2002;**11**:703-718

[17] Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. 2017;**1**:CD004143

[18] McNagny SE. Prescribing hormone replacement therapy for menopause symptoms. Annals of Internal Medicine. 1999;**131**:605-616

[19] Roberts H, Hickey M. Managing the menopause: An update. Maturitas. 2016;**86**:53-58

[20] Rodríguez-Landa JF, Hernández-Figueroa JD, Hernández-Calderón BC, Saavedra M. Anxiolytic-like effect of phytoestrogen genistein in rats with long-term absence of ovarian hormones in the black and white model. Progress in Neuropsychopharmacology and Biological Psychiatry. 2009;**33**(2):367-372

[21] Kageyama A, Sakakibara H, Zhou W, Yoshioka M, Ohsumi M, Shimoi K, Yokogoshi H. Genistein regulated serotonergic activity in the hippocampus of ovariectomized rats under forced swimming stress. Bioscience, Biotechnology and Biochemistry. 2010;**74**(10):2005-2010

[22] Jones AB, Gupton R, Curtis KS. Estrogen and voluntary exercise interact to attenuate stress-induced corticosterone release but not anxiety-like behaviors in female rats. Behavioral Brain Research. 2016;**311**:279-286

[23] Laven JS. Genetics of early and normal menopause. Seminars in Reproductive Medicine. 2015;**33**(6):377-387

Chapter 2

Menopause Female Reproductive Senescence from the Viewpoint of Evolutionary Anthropology

Sylvia Kirchengast

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68682

Abstract

Female reproductive senescence is characterized by the so-called menopausal transition taking place between the ages of 40 and 60 years. The major event of menopausal transition is menopause itself, which is biomedically defined as the cessation of menstrual function and the irreversible termination of female reproductive capability. Recent human females experience a postreproductive period from about 30 years. Such a long postreproductive period is absolutely uncommon among animals. Consequently, human menopause is still an evolutionary puzzle and several theories to explain the evolutionary basis of menopause have been presented. Menopausal transition, however, is also seen as a period of increased somatic and psychic symptoms which make this phase of life quite uncomfortable for affected women. In the present study, menopause and climacteric complaints are discussed from the viewpoint of evolutionary anthropology.

Keywords: menopause, human evolution, climacteric symptoms, reproductive senescence

1. Introduction

Recent *Homo sapiens* has the longest lifespan of all terrestrial mammals, however, human females stop to reproduce in the middle of it [1, 2]. Every woman who lives until about 50 years and beyond experiences the irreversible cessation of reproductive function, i.e., menopause. The World Health Organization (WHO) has defined menopause as the last spontaneous menstrual bleeding or the permanent cessation of menstruation resulting from loss of ovarian follicular activity [3]. Menopause is preceded by a phase of irregular cycles and starting hormonal changes, which is commonly called perimenopause. Perimenopause continued until 12 months after the last spontaneous menstrual bleeding, because no human female

knows exactly that the actual bleeding is really the last one [4]. Therefore, the phase of postmenopause is reached when a woman had no menstrual periods over 12 months. Menopause is a universal, one-time life event, which marks the transition from reproductive to postreproductive life in females [5]. Consequently, menopause is a marker of reproductive ageing patterns typical of the female *Homo sapiens* [6]. Menopause occurs usually between 45 and 55 years, recent human females, however, routinely live for about 30 years after the cessation of reproductive function [2]. Furthermore, reproductive senescence is markedly accelerated relative to general somatic aging among female *Homo sapiens* [7]. Even in traditional foragers societies such as the Ache, Hadza, or !Kung San, that do not enjoy the benefits of modern medicine women can expect 20 and more years of active life following menopause [8–10]. From the viewpoint of evolutionary biology, this extraordinary long postreproductive phase among human females is in strict contradiction to the biogenetic imperative and the paradigm that natural selection forces organisms to maximize reproductive success [11]. According to these assumptions, reproductive senescence and in particular menopause followed by a long postreproductive period should be rare in nature. In the present review, the phenomenon of menopause and extended postreproductive life span is focused on from the viewpoint of evolutionary anthropology, in particular, human life history theory. For an appropriate analysis of menopausal transition, we have to consider two different levels of causality in biology, i.e., proximate and ultimate explanations of biological phenomena [11]. Proximate causes are immediate mechanisms, such as physiological or ontogenetic factors, whereas ultimate explanations, in contrast, tried to interpret biological phenomena in an evolutionary sense [11]. Therefore, proximate as well as ultimate causes of menopause are discussed.

2. Human life history theory

As pointed out above, according to the biogenetic imperative and natural selection theory, menopause should be rare in nature. Among *Homo sapiens*, however, menopause is an obligatory part of female life history. Before we discuss menopause from the viewpoint of evolutionary anthropology, we have considered life history theory.

Every species has evolved its own patterns of ontogeny of the individual organism from conception to death. This species typical process contains somatic growth, development, maturation, reproduction, and senescence—all of them are energetically costly events [12]. Life history theory tries to explain the evolution of these patterns of growth and reproduction by identifying trade-offs [13]. An important trade-off is between somatic growth and the maintenance on the one hand and successful reproduction on the other. For most organisms, it is not possible to provide enough energy to grow and to reproduce simultaneously. Therefore many organisms have evolved a timely separation between growth and reproduction. A period where energy is provided for growth and development is followed by a period where energy is used for successful reproduction. Human life history differs from that of other social mammals in several puzzling details. Even our next living relatives, the nonhuman primates, exhibit marked differences in certain features of life history [14]. In detail, human infants are weaned relatively early, on average by age 36 months, but after weaning human children

depend on their mothers or other older group members for food and protection much longer than do the offspring of any other mammal, usually until they age about 7 years [12, 13]. From the viewpoint of evolutionary anthropology and human life history theory, the period between weaning and age of 7 years is defined as childhood stage, which is characterized by a set of biological and behavioral traits. This life history definition of childhood differs from the commonly used term childhood which refers to any time between birth and sexual maturation. It is assumed that the life history stage of childhood evolved about 2 million years ago among *Homo erectus*. The stage of childhood is not found among nonhuman primates [15]. Furthermore, humans reach puberty, i.e., sexual maturation, later than nonhuman primates and the short-term event of puberty is followed by an extended period of adolescence [15]. Adolescence is assumed to be a quite young stage of human life history occurring among *Homo sapiens* only. Since reproduction during early adolescence is rare, the interval between sexual maturation and first reproduction is much longer among humans than among nonhuman primates. Consequently, the age at first reproduction is much older than that of nonhuman primates; nevertheless human fertility may be higher than that among our nonhuman relatives. Modern humans however differ not only in the subadult stages of life history and reproductive success markedly from nonhuman primates and all other social mammals, the most distinct features are the extraordinary long life span and the prolonged period of female reproductive senescence, i.e., a long postmenopause [16]. During the fifth decade of life, fertility declines to essentially zero in human females; although one can expect to live for about further 30 years. This marked discrepancy between ovarian ageing and general ageing is a typical feature of female *Homo sapiens*. A prolonged postreproductive phase is not found among other animals, even among great social mammals with the exception of some toothed whale species.

3. Reproductive senescence among animals

As pointed out above, human females experience the cessation of reproductive function long before they die. Some signs of reproductive ageing are found among invertebrates in particular tephritid fruit flies [17] and the nematode *Caenorhabditis elegans* [18]. A kind of reproductive ageing characterized by a decline of sex steroid levels and a reduced probability of successful reproduction is found among several free living social mammals such as toothed whales, elephants, lions, or first of all primates [19–25]. An obligatory postreproductive life stage of 30 years and more, however, is exclusively found among human females [23]. Long postreproductive periods are uncommon among animals, even among large social mammals such as nonhuman primates and elephants. Only two Cetacean species such as short-finned pilot whales (*Globicephala macrorhynchus*) and killer whales (*Orcinus orca*) exhibit postreproductive life spans comparable to those of female *Homo sapiens* [22, 26]. Female short finned pilot whales stop to reproduce by about 36 years of age but they can live up to 65 years [22]. Female killer whales stop breeding by 48 years but they can live up to 90 years [22]. Baleen whales in contrast continue to reproduce into their nineties. Among large terrestrial mammals, elephants continue to reproduce into their sixties [27]. Quite difficult is the situation among our next living relatives, the nonhuman primates, because only few studies on

reproductive ageing patterns among wild living as well as captive primates exist. Some studies suggest that with increasing age a period of reproductive instability is quite common among female primates [28]. Data from *lemurs* and *callitriche* plead for age-related decline in reproduction in some species [28]. Furthermore, hormonal changes—comparable to menopausal hormonal transition among human females—have been noted in many primate species [24]. An increasing cycle length with increasing age was reported for captive chimpanzees but not for the wild chimpanzees [24]. The main problem is that nearly all studies of chimpanzees are based on very small samples and these studies have not provided clear conclusions. According to Thompson et al., there is no evidence that menopause is an obligatory characteristic of chimpanzee life history [29]. Data concerning Orangutan and Gorilla are still rare. Some evidence for an extended postreproductive phase exists for rhesus monkeys (*Macaca mulatta*) [24]. We can summarize that menopause and a long postreproductive phase is found exclusively among humans and some toothed whales. Consequently, menopause seems to be a typical feature of *Homo sapiens* and therefore we have to ask, why do human females loose the capability of reproduction much earlier than their next living relatives and most other social mammals?

4. Physiology of menopause: proximate approach

In the first step, we have to analyze the proximate or physiological basis of female reproductive senescence. From a proximate viewpoint, menopause results from follicular atresia that starts extremely early in female ontogeny, i.e., during intrauterine phase and continues until menopause [23, 30]. In the female embryo, primordial germ cells originating from the yolk sac develop into oogonia, immature sex cells. Germ cell numbers peak at approximately 3×10^5–7×10^6 by the fifth month of fetal development [31]. Oogonia develop to oocytes. Oocyte formation, however, ceases by the time a female fetus is 5 months old. Consequently, human females are unable to continue to produce oocytes past their fifth month in utero. At this time process of follicular degeneration and resorption from 3.4 to 7 million germ cells to less than 1000 remaining follicles at the time of menopausal transition, starts. The exorbitantly high number of 7 million oogonia declines to about 2 million oocytes at the time of birth and to about 400000 at pubertal onset. Oocytes are embedded in follicular cells. The vast majority of follicles are nonproliferating, produces steroids and succumb to atresia by apoptosis [23]. Only few follicles develop to preovulatory follicles with a thick layer of granulosa and theca cells, consequently only few oocytes undergo ovulation. The majority of follicles and oocytes, which are developmental units, degenerates before ovulation. Fertility declines in human females before total depletion of oocytes. A gradual decline in fertility is observable between the ages 35 and 40 years, after this period the decline accelerates. This reduced fertility from about 35 years onward is mainly due to defects in oocytes [31]. Oocyte or follicular depletion accelerates as menopause got closer. At the time of menopause, the activity of the few remaining follicles declines drastically [23].

The follicular decline results in marked hormonal disturbances typical of perimenopause and postmenopause [4]. The main feature of menopausal transition is the dramatic decline in

http://dx.doi.org/10.5772/intechopen.68682

estrogen levels [32, 33]. These hormonal disturbances are caused by the depletion of follicular cells. The theca and the granulosa cells of the follicle, however, are essential for estrogen synthesis in the ovary. Consequently, estrogens are no longer converted from androgen in the granulosa cells during menopausal transition [23]. The decrease of estrogen secretion resulted in consecutive disturbances of the hypothalamus-pituitary-gonad axis (HPO-axis). During reproductive phase, menstrual cycle patterns are regulated by this hormonal axis. The hypothalamus secretes gonadotropin releasing hormone (GnRh) directly to the anterior pituitary. The secretion patterns of GnRh are modified by neurotransmitters such as dopamine, serotonin, epinephrine, or endorphin. Receptors in the anterior pituitary sense the pulse frequency and amplitude of GnRh and direct the production of the gonadotropins, follicle stimulating hormone (FSH), and lutenizing hormone (LH), which are essential for reproduction. FSH stimulates follicle development, LH the estrogen synthesis in the ovaries. Both stimulate ovulation and LH induces corpus luteum development and in this way progesterone synthesis. FSH binds to specific hormone receptors on the membrane of the granulosa cells, whereas LH binds to receptors of the granulose and theca cells. Androgens are secreted under LH stimulation from the theca cells, in the granulosa cells these androgens are converted into estradiol. The hormone secretion of the HPO-axis is regulated by a negative feedback mechanism. During reproductive phase, female sex hormone secretion underlies dramatic cyclic fluctuations [32, 33].

Menopausal transition is characterized by marked endocrine changes which are mainly induced by changes within the ovary but also central neuroendocrine changes. The reduction of ovarian follicles during perimenopause results in declining levels of inhibin B, a dimeric protein, and a rise of follicle stimulating hormone (FSH) and lutenizing hormone (LH) levels. During perimenopause, estradiol levels remain relatively unchanged presumably in response to the elevated FSH levels [32, 33]. As the follicular supply is exhausted, estradiol (E_2) and estrone (E) decrease dramatically; FSH and LH, however, remain elevated. Estradiol, the most physiologically active estrogen, declines most markedly, whereas estrone continues to be produced through the conversion of androstenedione to estrone in muscle, adipose, and other tissues. Consequently, the hypothalamus-pituitary gonad axis (HPG-axis) is irreversible disturbed. Beside the decline in estrogens and progesterone (P), a decrease of testosterone (T), androstenedione (A), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and sex hormone binding globulin (SHBG) levels after menopausal transition was observed [32, 33]. Additionally, thyroxine (t_4) and triiodothyronine (t_3) levels as well as growth hormone (GH) decrease as a result of the general ageing process. This dramatic hormonal transition is often associated with weight gain and changes in body composition, in particular fat distribution patterns [34–41]. We can summarize from a proximate viewpoint that menopausal transition is caused by the final depletion of germ cells and it is characterized by marked hormonal disturbances which are associated with significant changes in body composition and fat patterning.

5. Evolutionary explanations of menopause: ultimate approach

According to Theodosius Dobzhansky, "nothing in biology makes sense except in the light of evolution" [42]. Consequently, we have to analyze menopausal transition from an ultimate

or evolutionary viewpoint. There is no doubt that menopause is clearly a biological phenomenon and consequently, we can assume that menopause has an evolutionary origin [43–45]. The majority of women in First world countries experience menopause usually between 47 and 55 years of life [46]. Considering an average life expectancy of about 80 years among females in First world countries, female postreproductive phase thus lasts on the average of 30 years. The potential maximum life span of recent *Homo sapiens* is even longer and is thought to be about 120 years. Considering this extraordinary long lifespan, we have to be aware that human females can spend more than half of their maximum life span potential with postreproductive period [23]. Such an extremely long postreproductive phase of life is unique in the animal kingdom and makes menopause to an extremely interesting event from an evolutionary point of view. If maximization of reproductive success is the ultimate goal of life, how can such a long postreproductive period be explained in evolutionary terms?

Since 1970s, several evolutionary scenarios of human menopause were proposed to explain the phenomenon of female reproductive senescence and in particular menopause; however, there is still no consensus about which of these hypotheses should be preferred [31, 45, 47, 48]. In general, two different types of evolutionary explanations of menopause can be distinguished: nonadaptive or by-product hypotheses and adaptive hypotheses [23]. Consequently, we have to ask that whether menopause is an adaption or an epiphenomenon [49].

At a first glimpse, the so-called by-product hypothesis seems comprehensible. The by-product hypothesis is based on the assumption that life expectancy increased dramatically during the last few centuries. In former times, however, the life expectancy was much shorter. Consequently, women did simply not live long enough to experience menopause for most time of our evolution and history. From a physiological point of view, menopause occurs when all oocytes are depleted. The maximum number of germ cells which is produced until fifth month in utero is adapted to a life expectancy of less than 50 years. According to the by-product hypothesis, it was assumed that in our past only few women lived until 50 years and beyond. Therefore, postmenopausal women did not exist. Consequently, menopause is not an adaptation, it is nothing else than a by-product of increased life span and therefore a very recent phenomenon [50, 51].

In contrast to by-product hypotheses, the adaptive hypotheses consider menopause itself as a fitness advantage [52]. The most important question is, how natural selection came to favor prolonged postreproductive phase in human life history? The antagonistic pleiotropy hypothesis—first proposed by Williams in 1957—suggests that if a gene caused both increased reproduction in early life and aging in later life, then reproductive senescence can be interpreted as adaptive. In case of menopause, it was assumed that follicular depletion may cause both more regular cycles in early life and loss of fertility in later life through menopause. Consequently, its early benefits may outweigh its late costs [53].

From the perspective of life history, the main question is, when in our evolution an extended postreproductive period occurred for the first time? At the moment, it seems that life circumstances of our ancestors changed dramatically about 2 or 1.8 million years ago at the time when *Homo erectus* lived [54]. At this stage of hominid evolution, new growth patterns and encephalization made a long dependency of offspring necessary and lead to life history patterns similar

http://dx.doi.org/10.5772/intechopen.68682

to those of recent *Homo sapiens,* such as introduction of childhood and also menopause and an extended period of postmenopause [54]. Consequently, it is assumed that menopause and prolonged reproductive senescence occurred first among *Homo erectus* about 2 million years ago [55]. Significantly associated with the existence of an extended postreproductive phase is the introduction with the life history stage of childhood between weaning and about 6 or 7 years of life. While weaned chimpanzees must forage for their own food, human children depend after weaning on older individuals for food and protection. This prolonged period of dependence during subadult phase of life makes an especially high parental investment necessary. Weaned children need extensive care because they are not able to use resources like adolescents and adults. Consequently, mothers have to provide a substantial fraction of their weaned children's diet [55]. Parents are often supported by the grandparents, first of all grandmothers, who provide a substantial investment in their grandchildren [56–58]. This is especially true for postmenopausal women with no young children of their own who help to feed and to take care of the offspring of their daughters and near relatives [55, 59]. This successful investment of postmenopausal women in related offspring, first of all grandchildren, suggests a solution to the riddle of prolonged postmenopausal period in humans. The so-called grandmother hypothesis as an evolutionary explanation of female menopause was a consequence of such ideas [60–62].

Human females are unable to reproduce after menopause; however, they invest in the offspring of their daughters and sons. In this way, a prolonged postreproductive span may have increased inclusive fitness of postmenopausal women. This point of view resulted in the introduction of the so-called grandmother hypothesis, which suggested increased fitness of women who stop reproduction and invest in their grandchildren [55, 61, 63–65]. The grandmother hypothesis is mainly based on the results of Kirsten Hawkes extensive fieldwork among Hadza hunter-gatherers northern Tanzania in eastern Africa [55, 60]. Nevertheless, the grandmother hypotheses have been criticized by several authors [66].

Beside the grandmother hypothesis, the so-called good mother hypothesis tries to explain the evolutionary benefit of an extended postreproductive phase in female *Homo sapiens*. The termination of reproductive capability independent of general senescence ensures that human females have a real chance to be young enough at their last birth to survive until their last offspring is able to survive without a biological mother [43, 67]. It is well documented that the survival of the mother during the rearing period is a major determinant of their children's survival. Considering subadult dependency in *Homo sapiens* mothers should survive until the last offspring reaches age of 7 years. According to Pavard et al. [52], menopause and subsequent postreproductive life are significantly advantageous when two conditions are satisfied: a marked increase in stillbirth and risk of birth defects as well as in maternal mortality with mother's age. Both the grandmother hypothesis and the "mother" hypothesis are the main adaptive explanations of human menopause. Female reproductive cessation seems to be a strategy that has been selected for during human evolution because women at older ages might maximize their fitness by investing resources in the survival and reproduction of their living offspring rather than by continuing to reproduce.

Recently, some new approaches to solve the evolutionary puzzle of menopause have been provided. According to the mate-choice hypothesis, male mating preference for younger females

may lead to the accumulation of mutations deleterious to female fertility and thus lead to the evolution of an extended postreproductive period in human females [68]. Takahashi et al. [31] tried to explain the origin and evolution of menopause by combining a genetic basis, behavioral factors such as mating behavior, a life history perspective, and social changes in human evolution.

Although many different theories to explain the origin and evolution of menopause have been presented, human menopause remains as an unsolved evolutionary puzzle.

6. Climacteric syndrome from the viewpoint of evolutionary anthropology

As pointed out above, menopause is a common experience of all human females who lived until about 50 years of age and beyond [23, 46, 69]. From a biological viewpoint, menopause simply reflects reproductive senescence, the end of childbearing phase and is therefore a natural part of female life history [5]. Consequently, menopause is not pathology because all human females who live long enough experience menopausal transition and the cessation of reproductive capability. Despite this fact, menopause was increasingly interpreted as a pathological condition since early nineteenth century. This medicalization of menopause within biomedical practice has affected the way menopause is viewed within society until today. Of special importance in this case is the work of the British gynecologist E.J. Tilt, who introduced the phenomenon of menopause in British Gynecology in 1857 [70]. In continental Europe and North America, biomedicine practitioners began to think of menopause as a disease-like state by the 1930s. As endocrinology improved and as synthetic estrogens became readily available in the 1960s, menopause was treated as a hormone deficiency disease, comparably to diabetes [71]. As a consequence, the medical (pathological) viewpoint dominates menopause research for a long time.

Two different approaches to this medical viewpoint can be distinguished: on the one hand, menopause is interpreted as an own deficiency disease or endocrinopathy. According to this view, hormonal deficiency results in symptoms of the so called climacteric syndrome [6, 71, 72]. This medicalization of menopause is mainly due to the fact that many women experience a large variety of symptoms, such as hot flushes and night sweats, and also psychic problems such as depression, irritability, or insomnia during peri- and postmenopause. This symptom complex is commonly called climacteric syndrome, which make peri- and postmenopause very uncomfortable for many women. In western societies, 60–70% of menopausal women reported hot flushes and night sweats [46, 69]. Climacteric symptoms seem to be strongly related to the menopause-specific decline of estrogen levels [32, 33]. However, not all climacteric women suffer from climacteric symptoms and the interpretation of the individual symptoms varies between individuals according to culture and society [46, 73–76]. Quite different is the alternative approach: menopause is not seen as a disease by itself but menopause is interpreted as a major risk factor for the development of other diseases such as osteoporosis, cardiovascular disease, some cancers such as breast cancer, and also Alzheimer disease [4, 77]. Additionally, the decline of estrogen levels after menopause enhances the risk of cardiovascular disease such as hypertension [78].

http://dx.doi.org/10.5772/intechopen.68682

Consequently, the risk of stroke, myocard infarct, and heart failure increases after menopause. Furthermore, menopause also seems to increase the risk of the development of certain cancers such as breast cancer [79, 80].

From the viewpoint of evolutionary anthropology, the so-called climacteric syndrome can be interpreted in an evolutionary sense. Of course, potential climacteric complaints cannot be reconstructed from fossil bones and it is not possible to search for climacteric complaints among nonhuman primates or other social mammals. However, different attitudes toward menopausal transition and climacteric symptoms are found in different cultural settings [73, 75, 76].

The climacteric syndrome, however, can also be interpreted from the viewpoint of evolutionary medicine [81, 82]. Evolutionary medicine was formalized in early 1990s, most notably by the evolutionary biologist George C. Williams and psychiatrist Randolph Nesse who tried to understand why natural selection has left the human body so vulnerable to diseases [83]. According to their concept, many medical conditions that are clearly pathological today have been adaptive in the ancestral environment in which *Homo sapiens* evolved. Evolutionary medicine is concerned with identifying and understanding these conditions in our environment of evolutionary adaptedness (EEA) [84]. Especially, the impact of changing living conditions during our evolution and also of more recent processes such as modernization and acculturation on health and disease is focused.

As pointed out above, we can assume that menopause and prolonged postmenopausal phase occurred first among members of *Homo erectus* about 2 million years ago [85]. In the first step, we have to look at the natural and social environment of our ancestors from about 2 million years ago up to 10,000 years ago when Neolithic transitions started. Ethnographic analyses of the few remaining contemporary forager populations such as the Hadza in Tanzania, the !Kung of Namibia and Botswana, Ache of Paraguay, or Efe of Central Africa provided information about diet and life style in recent foraging economy [8, 10]. The typical life style of foragers is highly mobile because high levels in daily activity in search of food, water, and sleeping sites are necessary. The diet consists mainly of lean meat, wild vegetables, tubers, berries, fruits, nuts, and roots, while excluding foods such as dairy products, grains, sugar, legumes, and fats. From a medical point of view, typical noncommunicable diseases such as hypertension, heart disease, cancer, type II diabetes, or obesity are rather unknown [86]. *Homo sapiens* is clearly adapted to an environment like this. With the emergence of agriculture in the area of the fertile crescent about 10,000 years ago, subsistence economy and life circumstances changed dramatically [87, 88]. Domestication of animals and plants allowed the production of a surplus of food, which resulted in population growth, and dietary changes [88]. Analyses of Neolithic skeletal remains indicated protein deficiencies and periodic food shortages, skeletal conditions which can clearly be interpreted as results of famine and starvation. Furthermore, the close proximity to domesticated animals exposed humans to a variety of new pathogens resulting in an increased frequency of infectious diseases [89]. Therefore, Neolithic transition has led to the so-called first epidemiologic transition [90]. A second epidemiologic transition occurred about 200 years ago during industrial revolution when a shift toward manmade diseases is observable.

During the twentieth and twenty-first century lifestyle changed again dramatically. Urbanization, technical advances, and general modernization resulted in a marked transition in human life style. Advances in medicine reduced human morbidity and mortality and lead to increased life expectancy. The daily energy effort to gather and prepare food is reduced nearly to zero, since only few individuals are working on food production. Mechanized transportation, sedentary jobs, and labor-saving household technologies reduce physical activity too. On the other hand, more than enough energy providing food, mainly consisting of sugar and fat is easily available [91, 92]. Consequently, a dramatic mismatch between current environment and human body evolved in the environment of our evolutionary adaptedness can be observed. In 99% of our evolutionary history, we have survived as foragers following a highly mobile life style in small groups. Obesity and noncommunicable diseases were quite unknown. Our gene pool was shaped by natural and sexual selection toward an optimal adaptation to these environments and life circumstances. Our recent environments, however, differ dramatically from that in which our ancestors evolved. There is no doubt that also some genetic changes had occurred since the Neolithic transition; however natural selection works slowly and our genome changed to a certain degree only. Therefore, we are still often adapted to a habitat that since more than 10,000 years no longer exists [83, 93–95].

Recent health problems such as climacteric complaints, cardiovascular disease, osteoporosis, or even postmenopausal breast cancer can be interpreted primarily as the results of a dramatic change in life style of women in contemporary societies. As pointed out above, the rapid decline in estrogen levels associated with menopause experienced by recent women in industrialized societies enhances climacteric symptoms such as hot flushes [23, 32, 33, 96]. These hormonal disturbances may be the result of our recent life style patterns. We have to be aware that life history patterns of contemporary women are unique within human evolution [65]. We can assume that female life history patterns in our environment of evolutionary adaptedness resemble those of contemporary hunter gatherer societies [65]. Recent female hunter gatherers reach sexual maturation quite late. Their reproductive span is characterized by many cycles of pregnancy, long periods of lactation, and early menopause. Consequently, the number of ovulatory cycles is quite low and about 100 ovulatory cycles are assumed during reproductive span. Therefore life-time estrogen levels were quite low [97]. These low levels of estrogens during adult life are caused by high levels of physical activity, a diet characterized by low fat contents, a low amount of body fat, and low body weight [79, 97]. Consequently, lifetime estrogen exposition was quite low in the environment of evolutionary adaptedness. Life history patterns of women in recent developed countries are quite different. Menarche occurs early and first pregnancy becomes late. In Austria, for example, first menstrual bleeding occurs at the age of 12 years on average, first birth, however, occurs at the age of 29.7 years [98]. This means a period of nearly 18 years between sexual maturation and first reproduction. Reproductive span of contemporary women living in First world countries is characterized by extremely few pregnancies, few births, and short periods of lactation. It can be assumed that a woman experiences about 400 cycles on the average. Menopause occurs late and hormone supply via hormonal contraceptives or hormone replacement therapy is usual. Consequently, life estrogen exposition is long and estrogen levels are high [99]. During menopausal transition, estrogen levels drop down very fast resulting in rapid hormone deficiency, which may lead to climacteric symptomatology [32, 33, 69].

Among recent traditional societies, following quite different life style patterns such as women in rural India or Maya women in Yucatan estrogen levels are very low during menopausal transition; nevertheless, climacteric symptoms are rarely reported. Traditional lifestyle is characterized by low life time estrogen levels. The decline of estrogen secretion during menopausal transition is therefore not as dramatic as among women in western societies. Sometimes, last lactational amenorrhea—characterized by low estrogen levels—switches to menopause [23]. Consequently, climacteric complaints as a reaction of a sudden drastic estrogen decline are prevented. The high prevalence of climacteric symptoms in western societies may therefore be interpreted as a result our recent life style.

Additionally, a high rate of physical activity and a traditional diet poor in fat reduce estrogen levels through reproductive phase and even during and shortly after menopausal transition. Estrogens are converted from androgens in adipose tissue. Consequently, a higher amount of body fat increase the estrogen levels during reproductive phase and even during menopausal transition. This positive association between body fat and estrogen levels increases also the probability to develop breast cancer during peri- and postmenopause. A sedentary life style, high fat contents in diet, high life time estrogen levels, and high rates of overweight and obesity during middle age increase the risk of several diseases associated with menopausal transition such as breast cancer, cardiovascular disease, and also osteoporosis [100].

7. Conclusion

From the viewpoint of evolutionary anthropology, menopause is a natural part of female life history and therefore not a pathology. Several theories have been proposed to explain the evolutionary basis of menopausal transition, although there is still no consensus. The climacteric syndrome—mainly caused by estrogen deficiency—may be interpreted as the result of a mismatch between recent life style and reproductive patterns and life circumstances in the environment in which our ancestors evolved.

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References

[1] Fernell RJ, Sowers MF. Longitudinal, epidemiologic studies of female reproductive aging. Annals of the New York Academy of Sciences 2010, **1204**:188-197

[2] Gold EB. The timing of the age at which natural menopause occurs. Obstetrics and Gynecology Clinics of North America. 2011;**38**:425-440

[3] World Health Organization (WHO). Research on Menopause in the 1990s. WHO Technical Reports Series No. 866. Geneva: WHO 1996

[4] Huber JC. Klimakterium – Diagnose und Therapie. Berlin: Berliner Medizinische Verlagsanstalt; 1995

[5] Melby MK, Lampl M. Menopause a biocultural perspective. Annual Review of Anthropology. 2011;**40**:53-70

[6] Utian WH. Overview of menopause. American Journal of Obstetrics & Gynecology. 1987;**156**:1280-1283

[7] Pavelka MSM, Fedigan LM. Menopause: A comparative life history perspective. Yearbook of Physical Anthropology. 1991;**34**:13-38

[8] Howell N. Life Histories of the Dobe !Kung. Food, Fatness and Well Being Over the Lifespan. Los Angeles: University of California Press; 2010

[9] Hill K, Hurtado AM. Ache Life History. The Ecology and Demography of a Foraging People. New York: de Gruyter; 1995

[10] Marlowe FW. The Hadza Hunter Gatherers of Tanzania. Los Angeles: University of California Press; 2010

[11] Voland E. Grundriss der Soziobiologie. Stuttgart: Fischer Verlag; 1993

[12] Hill K, Kaplan H. Life history traits in humans. Theory and empirical studies. Annual Review of Anthropology. 1999;**28**:397-430

[13] Bogin B, Smith H. Evolution of the human life cycle. American Journal of Human Biology. 1996;**8**:703-716

[14] Holland Jones J. Primates and the evolution of long-slow life histories. Current Biology. 2011;**21**:708-717

[15] Bogin B. Evolutionary hypotheses for human childhood. Yearbook of Physical Anthropology. 1997;**40**:63-89

[16] Kuzawa CW, Bragg JM. Plasticity in human life history strategy: Implications for contemporary human variation and the evolution of Genus *Homo*. Current Anthropology. 2012;**53**:S369-S382

[17] Carey JR, Molleman F. Reproductive ageing in tephritid fruit flies. Annals of the New York Academy of Sciences. 2010;**1204**:139-148

[18] Kenyon C. A pathway that links reproductive status to lifespan in Caenorhabditis elegans. Annals of the New York Academy of Sciences. 2010;**1204**:15-162

[19] Austad SN. Animal models of reproductive aging: What can they tell us? Annals of the New York Academy of Sciences 2010, **1204**:123-128

[20] Altmann I, Gesqiere L, Galbany J, Onyango PO, Alberts SC. Life history context of reproductive aging in a wild primate model. Annals of the New York Academy of Sciences. 2010;**1204**:127-138

[21] Hawkes K, Smith KR. Do women stop early? Similarities in fertility decline in humans and chimpanzees. Annals of the New York Academy of Sciences. 2010;**1204**:43-53

[22] Johnston RA, Cant MA. The evolution of menopause in cetaceans and humans: The role of demography. Proceedings. Biological Sciences. 2010;**22**:3765-3771

[23] Leidy-Sievert L. Menopause. A Biocultural Perspective. London: Rutgers University Press; 2006

[24] Walker MI, Herndon JG. Menopause in non human primates. Biology of Reproduction. 2008;**79**:398-406

[25] Ward EJ, Parson K, Holmes EE, Balcom KC, Ford JLB. The role of menopause and reproductive senescence in a long lived social mammal. Frontiers in Zoology. 2009;**6**:4-14

[26] Brent LJN, Franks DW, Foster EA, Balcomb KC, Cant MA, Croft DP. Ecological knowledge, leadership, and the evolution of menopause in Killer whales. Current Biology. 2015;**25**:746-750

[27] Moss CJ. The demography of an African elephant (*Loxodonta Africana*) population in Amboseli Kenya. Journal of Zoology. 2001;**255**:145-156

[28] Atsalis S, Margulis S. Primate reproductive ageing: From lemurs to humans. Interdisciplinary Topics in Gerontology 2008;**36**:186-194

[29] Thompson ME, Jones JH, Pusey AE, Brewer-Marsden S, Goodall J, Marsden D, Matsuzawa T, Nishida T, Reynolds V, Sugiyama Y, Wrangham RW. Ageing and fertility patterns in wild chimpanzees provide insights into the evolution of menopause. Current Biology. 2007;**17**:2150-2156

[30] Finch Ce, Homes DJ. Ovarian aging in developmental and evolutionary contexts. Annals of the New York Academy of Sciences 2010, **1204**:82-94

[31] Takahashi M, Singh RS, Stone J. A theory for the origin of human menopause. Frontiers in Genetics.2016, **7**:1-12

[32] Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. Recent Progress in Hormone Research. 2002;**57**:257-275

[33] Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: Focus on findings from the Melbourne Women's Midlife Health project. Human Reproduction Update. 2007;**13**:559-565

[34] Astrup A. Physical activity and weight gain and fat distribution changes with menopause: Current evidence and research issues. Medicine & Science in Sports & Exercise. 1999;**31**:S564-S567

[35] Douchi T, Yamamoto S, Yoshimitsu N, Andoh T, Matsuo T, Nagata Y. Relative contribution of ageing and menopause to changes in lean and fat mass in segmental regions. Maturitas. 2002;**42**:301-306

[36] Douchi T, Yamamoto S, Nakamura S, Ijuin T, Oki T, Maruta K, Nagata Y. The effect of menopause on regional and total body lean mass. Maturitas. 1998;**29**:247-252

[37] Tchernof A, Poehlmann ET. Effects of the menopause transition on body fatness and body fat distribution. Obesity Research. 1998;**6**:246-254

[38] Panotopoulus G, Ruiz JC, Raison J, Guy-Grand B, Basdevant A. Menopause, fat and lean distribution in obese women. Maturitas. 1996;**25**:11-19

[39] Messier V, Rabasa-Lhoret R, Barat-Artigar S, Elisha B, Karelis AD, Aubertin-Leheudre M. Menopause and sarcopenia: A potential role for sex hormones Maturitas. 2011;**68**:331-336

[40] Piche ME, Lapointe A, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J, Lemieux S. Regional body fat distribution and metabolic profile in postmenopausal women. Metabolism – Clinical and Experimental. 2008;**57**:1101-1107

[41] Kirchengast S, Gruber D, Sator M, Hartmann B, Knogler W, Huber J. menopause associated differences in female fat patterning estimated by dual-energy-x-ray absorptiometry. Annals of Human Biology. 1997;**24**:45-54

[42] Dobzhansky T. Nothing in Biology makes sense except in the light of evolution. The American Teacher. 1973;**35**:125-129

[43] Sherman PW. The evolution of menopause. Nature. 1998;**392**:759-760

[44] Shanley DP, Sear R, Mace R, Kirkwood TBL. Testing evolutionary theories of menopause. Proceedings of the Royal Society B: Biological Sciences. 2007;**274**:2943-2949

[45] Pollycove R, Naftolin F, Simon JA, The evolutionary origin and significance of menopause. Menopause. 2011;**18**:336-342

[46] Palacios S, Henderson VW, Siseles N, Viaseca P. Age of menopause and impact of climacteric symptoms by geographical region. Climacteric. 2010;**13**:419-428

[47] Peccei JS. The origin and the evolution of menopause: The altriciality-lifespan hypothesis. Ethology and Sociobiology. 1995;**16**:425-449

[48] Wu JM, Zelinski MB, Ingram DK, Ottinger MA. Ovarian Ageing and menopause: Current theories, hypotheses and research models. Experimental Biology and Medicine. 2005;**230**:818-828

[49] Peccei JS. Menopause: Adaptation or epiphenomenon? Evolutionary Anthropology. 2001;**12**:43-57

[50] Washburn S. Longevity in primates. In: McGaugh JMJ, editors. Aging, Biology and Behaviour. New York: Academic Press; 1981. pp. 11-29

[51] Weiss KM. Evolutionary perspectives on human aging. In: Amoss PT, Harell S, editors. Other Ways of Growing Old. Stanford: Stanford University Press; 1981. pp. 25-58

[52] Pavard S, Metcalf CIF, Heyer E, Senescence of reproduction may explain adaptive menopause in humans. American Journal of Physical Anthropology. 2008;**136**:194-203

[53] Wood JW, O'Conner KA, Holman DJ, Bringle E, Barsom SH, Grimes MA. The evolution of menopause by antagonistic pleiotropy. Center for Demography and Ecology; 2001 (Working Paper)

[54] Bogin B. Patterns of Human Growth. Cambridge: Cambridge University Press; 1999

[55] Hawkes K, O'Connell JF, Blurton Jones NG, Alvarez H, Charnov AL. Grandmothering, menopause and the evolution of human life histories. Proceedings of the National Academy of Sciences. 1998;**95**:1336-1339

[56] Sear R, Mace R. Who keeps children alive? A review of the effects of kin on child survival. Evolution and Human Behavior. 2008;**29**:1-18

[57] Sear R. Kin and child survival in rural Malawi. Human Nature. 2008;**19**:277-293

[58] Coall DA, Hertwig R. Grandparental investment: Past, present, and future. Behavioral and Brain Sciences. 2010;**33**:1-59

[59] Sear R, Mace R, McGregor I A. Maternal grandmothers improve nutritional status and survival of children in rural Gambia. Proceedings of the Royal Society. 2000;**267**:1641-1647

[60] Hawkes K, O'Connell JF, Blurton Jones NG. Hadza women's time allocation, offspring provisioning and the evolution of long postmenopausal lifespans. Current Anthropology. 1997;**38**:551-577

[61] Hawkes K. Grandmothering of human longevity. American Journal of Human Biology. 2003;**15**:380-400

[62] Lahdenperä M, Lummaa V, Helle S, Tremblay M, Russell AF. Fitness benefits of prolonged post-reproductive lifespan in women. Nature. 2004;**428**:178-181

[63] Alvarez HP. Grandmother hypothesis and primate life histories. American Journal of Physical Anthropology. 2000;**113**:435-450

[64] Voland E, Chasiotis A, Schiefenhövel W. Grandmotherhood. The Evolutionary Significance of the Second Half of Female Life. New York: Rutgers University Press; 2005

[65] Blurton Jones NG, Hawkes K, O'Connell JF. Antiquity of postreproductive life. Are there modern impacts on hunter gatherer postreproductive life span. American Journal of Human Biology. 2002;**14**:184-202

[66] Peccei JS. A critique of the grandmother hypotheses: Old and new. American Journal of Human Biology. 2001;**13**:434-452

[67] Alexander RD. The evolution of social behaviour. Annual Review of Ecology and Systematics. 1974;**5**:325-383

[68] Morton RA, Stone JR, Singh RS. Mate choice and the origin of the menopause. PLoS One. 2013;**9**:e1003092

[69] Hunter M, Rendall M. Bio-psycho-socio-cultural perspectives on menopause. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2007;**21**:261-274

[70] Van de Wiel L. The time of the change: Menopause's medicalization and the gender politics of aging. International Journal of Feminist Approaches to Bioethics. 2014;**7**:74-98

[71] McCrea FB. The politics of menopause: The discovery of a deficiency disease. Social Problems. 1983;**31**:111-123

[72] Bell SE. Changing ideas: The medicalization of menopause. Social Science & Medicine. 1987;**24**:535-542

[73] Beyene Y, Cultural significance and physiological manifestations of menopause: A biocultural analysis. Culture Medicine and Psychiatry. 1986;**10**:47-71

[74] Lock M. Encounters with Aging: Mythologies of Menopause in Japan and North America. Berkeley: University of California Press; 1993

[75] Kilaf E, Kirchengast S. Menopause between nature and culture: Menopausal age and climacteric symptoms among Turkish immigrant women in Vienna, Austria. Acta Medica Lituanica. 2008;**15**:313-329

[76] Pitkin J. Cultural issues and the menopause. Menopause International. 2010;**16**:156-161

[77] Worcester N, Whatley MH. The selling of HRT: Playing on the fear factor. Feminist Review. 1992;**41**:1-26

[78] Mayo JL. A natural approach to menopause. Applied Nutritional Science Reports. 1997;**5**:1-8

[79] Turner LB, A meta-analysis of fat intake, reproduction and breast cancer risk: An evolutionary perspective. American Journal of Human Biology. 2011;**23**:601-608

[80] Wu AH, Pike MC, Stram DO. Meta-analysis: Dietary fat intake, serum estrogen levels and the risk of breast cancer. Journal of the National Cancer Institute. 1999;**91**:529-534

[81] Froehle AW. Postmenopausal health and disease from the perspective of evolutionary medicine. Anthropology &Aging Quarterly. 2013;**34**:61-86

[82] Kirchengast S, Rühli F. Evolutionary medicine and its implications for endocrinological issues (e.g. menopause). Comparative Endocrinology 2013, **186**:145-149

[83] Nesse RM, Stearns SC. The great opportunity: Evolutionary applications to medicine and public health. Evolutionary Applications. 2008;**1**:28-48

[84] Bowlby J. Attachment and Loss. New York: Basic Books; 1969

[85] Henke W, Hardt T. The genus *Homo*: Origin, speciation and dispersal. In: Condemi S, Weniger G-C, editors. Continuity and Discontinuity in the peopling of Europe: One hundred fifty years of Neanderthal study, Vertebrate Paleobiology and Paleoanthropology. New York: Springer Press; 2011. pp. 17-43

[86] Eaton SB, Konner M. Paleolithic nutrition: A consideration of its nature and current implications. New England Journal of Medicine. 1985;**312**:283-289

[87] Maher LA, Richter T, Macdonald D, Jones MD, Martin L, Stock IT. Twenty thousand year old huts at a hunter gatherer settlement in eastern Jordan. PLoS One 2012;**7**:e31447

[88] Larsen C. Biological changes in human populations with agriculture. Annual Review of Anthropology. 1995;**24**:185-213

[89] Armelagos GI, Goodman AH,.Jacobs KH. The origins of agriculture: Population growth during a period of declining health. Population and Environment. 1991;**13**:9-22

[90] Barrett R, Kuzawa CW, McDade T,.Armelagos GI. Emerging and re-emerging infectious diseases: The third epidemiologic transition. Annual Review of Anthropology. 1998;**27**:247-271

[91] Popkin BM, Gordon-Larsen P. The nutrition transition: Worldwide obesity dynamics and their determinants. International Journal of Obesity. 2004;**28**:52-59

[92] Lieberman LS. Evolutionary and anthropological perspectives on optimal foraging in obesogenic environments. Appetite. 2006;**47**:3-9

[93] Trevathan WR. Evolutionary medicine. Annual Review of Anthropology. 2007;**36**: 139-154

[94] Vitzthum VI, Evolutionary models of women's reproductive functioning. Annual Review of Anthropology. 2008;**37**:53-73

[95] Wick G, Berger P, Jansen-Dürr P, Gerbeck-Loebenstein B. A Darwinian-evolutionary concept of age-related diseases. Experimental Gerontology. 2003;**38**:13-25

[96] Santoro N. The menopause transition: An update. Human Reproduction Update. 2002;**8**: 155-160

[97] Eaton SB, Pike MC, Short RV, Lee NC, Trussell J, Hatcher RA, Wood JW, Worthman CM, Nicolas GBI, Konner MJ, Bailey R, Hurtado AM, Women's reproductive cancers in evolutionary context. The Quarterly Review of Biology. 1994;**69**:353-3657

[98] Statistik Austria. Demographic Yearbook. Vienna, Austria. 2016

[99] Shaw LAM, Shaw SLJ, Menopause, evolution and changing cultures. Menopause International. 2009;**15**:175-179

[100] Strassmann BI. Menstrual cycling and breast cancer: An evolutionary perspective. Journal of Women's Health. 1999;**8**:193-202

Chapter 3

Menopause in Nonhuman Primates: A Comparative Study with Humans

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69657

Abstract

Although menopause is a phenomenon predominantly studied in humans or laboratory animals, this chapter discussed the case of nonhuman primates (NHPs), not only with the objective of employing them as study models but also to better understand phylogenetic divergence among species. Those taxonomic differences are reflected in reproductive processes that may be similar to those of human beings, with the presence of a defined cycle or periods of estrus, but perhaps at different ages as well, where menopause plays a crucial role. First, it is important to delimit the concept of menopause by considering its anatomical, physiological, and biochemical parameters, including the cessation of menstrual bleeding or perineal swelling—when present—or follicular depletion and hormonal changes. Thus, the aim of this chapter is to discuss some of the similarities between NHPs and human females, during the menopause period. Studying these phenomena should help us achieve a better understanding of the social, physiological, and environmental factors without adopting any particular cultural view of menopause.

Keywords: nonhuman primate, ovarian cycle, reproductive cessation, new world monkeys, old world monkeys

1. Introduction

Menopause is a process of the reproductive aging [1] manifested in the depletion of ovarian follicles, the reduction of ovarian hormones to castration levels, and the increase in the concentration of serum gonadotropins [2]. In human beings, this process occurs in midlife, heralded by the gradual disappearance of menstrual cycles accompanied by the end of reproductive capacity, which correlates with functional and structural changes in the hypothalamic-pituitary-ovarian axis [3].

This process is not exclusive to humans, for it also occurs in all iteroparous organisms that exhibit declining fertility as a function of general senescence [4]. However, in contrast to human beings, nonhuman primates (NHPs) and even longer lived species like tortoises, elephants, and whales retain their capacity to reproduce until relatively advanced age [5]. Studies in NHPs, such as monkeys and apes, both in the wild and in conditions of captivity, have reported menopause as a physiological phenomena [6–8], but they clearly show that the reproductive changes observed in NHPs differ from those of human menopause, at least from a perspective of comparative life history [6]. This is because most of the oldest individuals in all wild species studied showed no signs of ovarian failure, while studies of captive primate species have observed that 67% of old females continued reproducing throughout their lives [7].

It has been suggested that the differences between the human fertility pattern and those of other NHPs are evident in the maximum age of reproduction and mean life expectancy at maturity of both. This refers to the fact that human beings have an early fertility peak that begins to decrease when they are in their mid-1920s, followed by a general decline and then a steep drop that normally begins around age 35; being this age the specific moment fertility functions of NHPs as macaques remain relatively constant over a long period, terminating abruptly only a few years before age death [9].

NHPs are used in medical and scientific research due to their similarities in physiology, neuroanatomy, reproduction, development, cognition, and social complexity to humans, which reflect their close phylogenetic relationship between NHPs and human beings. Primates are divided phylogenetically into strepsirrhines (galagos, lorises, and Malagasy lemurs) and haplorhines (tarsiers and anthropoids). There are three major branches of extant anthropoids or higher primates: the Platyrrhini or New World monkeys (South and Central America) and two groups of Catarrhini (the Cercopithecoids or Old World monkeys (Africa, Europe, and Asia) and Hominoids (Apes and human beings)) (**Figure 1**) [10].

The aim of the present chapter is to discuss and analyze some similarities between female NHPs and human females during natural or surgically induced menopause, since expanding our knowledge of this phenomenon in mammals with such a close phylogenetic relationship so to human beings should lead to a more comprehensive understanding of this biological process.

http://dx.doi.org/10.5772/intechopen.69657

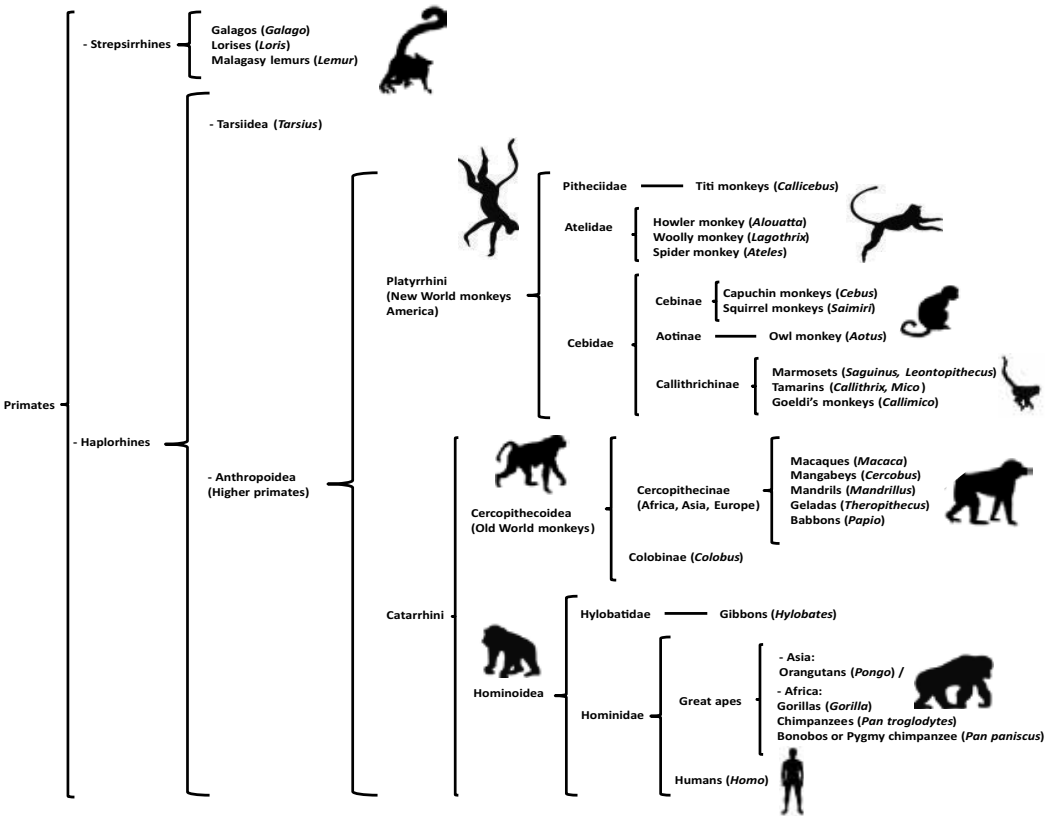

Figure 1. Taxonomic classification of extant primates with branch lengths in millions of years. Representative genus is shown in brackets (modified from Ref. [10]).

2. Reproductive cycles in nonhuman primate females and their relation with cycles in human beings

For many mammals, estrus is not only confined to a brief portion of the reproductive cycle that is characterized by an increase in attractivity and in the proceptive and receptive behaviors of females but is also strictly seasonal. In NHPs the reproductive cycles occur for only a few weeks of the year, as occurs among Madagascar prosimians, such as the sifakas. In some New World primates, such as squirrel monkeys, sexual cycles occur only during 3 months of the year [11], but many catarrhine primates do not follow this strict pattern circumscribed by the estrous period [12]. The literature mentioned that apes, human beings, and many monkeys have reproductive cycles that differ in two ways: first, the cycles include menstruation, a cyclical sloughing of the uterine lining. Second, there is greater flexibility in the time of proceptive and receptive behaviors with a longer duration of estrus [13]. Apes and Old World

monkeys, meanwhile, exhibit menstrual cycles that range from 25 to 35 days similar to those human females. Also in NHPs, mating activity is not restricted to the periovulatory period as occurs in other mammals since female receptivity is not under strict control of ovarian hormones, but is more closely related to the social context, also as in human beings [14]. Finally, circulating steroid hormones reflect the process of ovulation and ovarian cycling [15].

2.1. Ovarian cycle in nonhuman primates

Ovarian cycles in primates begin with a follicular phase during which the follicle matures, follicular secretion of estrogen increases, and the circulating concentration of progesterone (P_4) decreases [16]. In most primates, only one follicle ovulates in each cycle. It emerges during the mid-follicular phase and inhibits maturation of other follicles by secreting large amounts of estrogen that, in turn, reduce concentrations of the follicle-stimulating hormone (FSH) below the threshold level required for maturation of early antral follicle [17]. Second, ovulation occurs immediately after the follicular phase, and this maintains high circulating concentrations of estrogens from the mature follicle while exerting positive feedback on the hypothalamus and pituitary that triggers secretion of the gonadotropin-releasing hormone (GnRH), as well as FSH and luteinizing hormone (LH). The increased LH reaches the ovaries where it causes the follicle to rupture [18]. Third, during the luteal phase, the concentration of P_4 rises, but that of estrogens declines. Fertilization can take place during the early luteal phase of the cycle only during the first 24 h after ovulation. This is because the oocyte has a short life span. If the ovum is fertilized, then the corpus luteum does not degrade and continues to secrete P_4 until the placenta develops [19].

Some of these processes are similar to the ovarian cycles in the human beings [20]; however, studies have found that in all primate species studied, follicular development, ovulation, and corpus luteum formation occur spontaneously and independent of mating-induced stimuli [21]. Also, NHPs have been shown to have extended ovarian cycles, especially prolonged luteal phases, compared to those of other mammals [22]. Also, the duration of the follicular and luteal phases differs among NHPs. Cycle lengths vary among different primate groups: in prosimians, from 30 to 50 day; in New World monkeys, from 16 to 30 days; in Old World monkeys, from 24 to 35 days; in lesser apes, from 20 to 30 days; and in great apes—including humans—from 25 to 50 days [14, 15, 21, 23]. In contrast, squirrel monkeys have a mean cycle length of just 7–12 days, with a follicular phase of about 5 days [24].

Menstruation appears to be absent in all prosimians and possibly in tarsiers, presumably associated with the noninvasive form of placentation characteristic of these primates [21]. However, menstruation does occur in most Old World monkeys and apes, as well as in several New World monkeys [25], and prosimians may be considered to have an estrous cycle, because they exhibit distinct cyclical changes in relation to sexual receptivity, with a peak during the periovulatory period. Finally, many New World monkeys do not exhibit either menstruation or strict estrous cyclicity [20].

2.2. Ovarian cycle in humans

In human beings menstrual bleeding is the visible sign of cyclicity; it has a length of 3–6 days and occurs at the end of the luteal phase and the beginning of the follicular. While fertile phase

has a length of 5 days and is associated with the end of follicular phase and an increase of estradiol (E_2) before ovulation, during this period conception can occur. Recent studies have found that human females possess dual sexuality, which consists of a fertile phase where they are more sexually attractive to men and a phase extended (non-fertile), which presents a motivation or interest in sex with the aim of obtaining some benefits, without conception occurring [26].

2.3. Reproductive aging

Female reproductive output differs markedly in relation to species and time. As females of many species age, a period of reproductive instability with perimenopausal-like hormonal changes has been observed. Like many other mammals, NHP females show fertility parameters that are related to age [7]. Anovulation, insufficient luteolysis, and impairment of gestation and lactation processes all become more common toward the end of reproductive life [27]. Female reproductive senescence differs among mammalian taxonomic groups. For example, in NHPs, the end of reproductive life is characterized by the loss of the follicular pool, whereas in rodents, variations are seen in the size of the follicular pool that remains at the end of reproductive life. In humans, experiencing follicular depletion early in the maximum life span is not usual; rather, it is the result of an extended period of altered hormonal environments. These alterations may be caused by reduced circulating estrogens, P_4, and inhibin, resulting in elevated gonadotropin concentrations (GTHs) for a time, followed by their decline [28]. Monkeys and apes also experience follicular depletion and associated hormonal alterations [8, 29], but the stage of life at which these occur is generally later than in humans. Some reports on lemurs and callitrichids indicate an age-related decline in reproduction in many species that is reflected in diminished reproductive success [30]. Older female sifakas (*Propithecus edwardsi*), a Madagascar lemur, show decreased rates of infant survival, and studies have affirmed that this effect can be attributed to the females' deteriorating dentition resulting in inability to support lactation [31]. This indicates that reduced fertility in old age does not, in and of itself, reflect impaired neuroendocrine or gonadal function [20].

Considering the taxonomic scale of primates, we can observe the variability in physiological characteristics, like it is reflected in aging process. As much NHPs get closer to human beings, more similarities are found, going through estrous cycles for strepsirrhines (galagos, lorises, and lemurs), to ovarian cycles, and hormonal profiles similar to human being females, in great apes (orangutans, gorillas, and chimpanzees), and Old World monkeys (macacos and baboons). Also in both cases, at the end of their reproductive life, different physiological and hormonal changes occur, which are associated with the loss of ovarian function that are characteristic of aging, where this gives us the opportunity to study in a comparative way different alterations that could be related to the absence of ovarian hormones.

3. Menopause in *Homo sapiens* females and nonhuman primates

Menopause has been defined as a series of changes in the termination of reproductive viability, of which the discontinuation of menstruation is but one component. Menstrual bleeding is a marker of the ovarian and neuroendocrine phenomena of reproductive viability in

humans [32], but not all NHPs exhibit this [24]. Consequently, menopause must encompass hormonal, physiological, and biochemical changes that play essential roles in the cessation of ovarian cyclicity, regardless of whether menstrual bleeding is present. However, Walker and Herndon [1] have defined menopause in NHPs as the permanent, non-pathological, age-associated cessation of ovulation, so to infer this event would require considering such biological parameters as menstrual bleeding, perineal swelling, follicular depletion, and hormonal changes.

Some species of NHPs seem to present processes that are quite similar to what human females experience during menopause, but differences also exist, such as the shorter postmenopausal life span and differences in the timing of hormonal changes during the menopausal transition [33]. It is important to consider the time of menopause relative to the average and maximum life span of individuals. For example, humans may be unique among primates in that they have a long post-reproductive survival potential [34]. In human females, the reproductive function does not begin with puberty nor does it end with menopause at a certain chronological age. Instead, both of these are dynamic periods for the reproductive axis, during which development or senescence occurs relatively rapidly. In fact, the reproductive axis ages to a nonfunctional state (menopause) much earlier than other organs, while the reproductive system reaches the point of failure at a relatively young average age of 51 + 8 years [35]; considering that the maximum span for humans is around 80 years, they spend nearly 35% of her life in a post-reproductive state and in very special cases to 60% (122 years). Also, there are significant differences between species of NHPs and humans in terms of life span. For example, the life span of animals after menopause is short compared to humans, as they usually die not long after menopause [1].

Human females are born with a finite number of oocytes; thus, reproductive aging entails the steady loss of these oocytes through atresia and ovulation, processes that do not necessarily occur at constant rates [36]. Peak fertility in humans occurs in the mid-20s, after which it declines steadily until a steep decrease begins after age 35 [37]. This decline in fertility occurs despite normal hormone secretion by the ovaries of "older" reproductive-age humans, which continues until 3–4 years prior to menopause [38].

In spite of the wide age range at which ovarian dysfunction and reproductive failure occur in these species, the sequence of terminal events is fairly predictable. At the beginning of the process, the menstrual cycle length is shortened due to early follicular development and ovulation [39], which reduces fertility (premenopause). This is followed by disruption of regular menstrual cyclicity (perimenopause) and, finally, complete ovarian failure (menopause). Studies have observed that perimenopause is an indication that the number of remaining ungrown ovarian follicles has dropped below a critical threshold [40]. The period of transition from the reproductive phase to the nonreproductive state is called climacteric. Finally, postmenopause is the period following climacteric and occurs when the hormonal instability that characterizes perimenopause is replaced by the relative stability of the post-reproductive life stage when the reproductive function has ceased [41].

Declining fertility with age is manifested more commonly in monkeys and apes, to the point that some females cease to reproduce altogether before they die. Some reports on Old World

monkeys in the wild mention that old toque macaque (*Macaca sinica*) and gray-cheeked mangabey (*Lophocebus albigena*) females no longer breed, perhaps due to increasingly long birth intervals that terminate with death or the cessation of ovulation [42]. In contrast, NHP females living in captivity may show life cycles marked by irregular and lengthened menstrual cycles, reduced estrogen levels, very long birth spacing and, in a few cases—such as chimpanzees—total cessation of ovulation [8, 43]. In captive rhesus monkeys (*Macaca mulatta*), menstruation ends at approximately 25 years of age [44], and their maximum life span is around 30 years [45]; thus, this species may have a maximum post-reproductive life span of approximately 20%, similar to what happens in chimpanzees (*Pan troglodytes*). There are also differences in life span among species of NHPs and humans. For example, the life span of other animals after menopause is short compared to humans, since they usually die after only a short time, while humans have an extended postmenopausal life expectancy [1].

The perimenopause period is also highly variable in human beings, as age at the onset of this period ranges from the mid-1930s to the early 1950s [46]. This wide range impedes gaining a better understanding of the mechanisms that control the onset of menopause in humans. In NHPs, this is even more difficult, since reproductive cessation occurs so late in their life span that relatively few individuals actually live to those ages. However, there are data that support the existence of a perimenopausal in NHPs [33, 47–49], a condition that indicates a transitional stage between fertility and age-associated infertility. Also, it has been reported that patterns of vaginal bleeding and serum hormone profiles of macaques in the third decade of life are similar to those described for peri- and postmenopausal human [29].

Although originally the term menopause was coined in human being context, there are some approaches toward NHPs, which let us build it, considering not only the cessation of menstrual bleeding but also other changes, such as the cessation of perineal swelling, follicular depletion, and hormonal-associated changes. So this term has been adapted focusing in the physiological characteristics of each species. By other hand the life span between species should be considered, because unlike human beings, some species usually transit immediately from the reproductive end to death. Therefore, it is of great importance to know what are the differences between species that could help us identify the age of onset of menopause according to the species of the study, and, since this information, it will depend on whether or not our data can be extrapolated to the human.

4. Menopause in nonhuman primates in wild versus captive conditions

Specific studies over physiological mechanisms that govern the timing of menopause in wild NHPs are scarce [42, 50], because many factors could mask the accuracy of these results, including the ages of subjects—which often must be estimated [51]—predation pressures [52], limited survivability [23], infant mortality [53], food availability and nutrition [54], and social dynamics [55]. Therefore, this information is taken as complementary to data derived from captive animals [1].

4.1. Macaques (*Macaca* spp.)

Hodgen et al. [29] reported that female rhesus monkeys (*Macaca mulatta*), in captivity and at least 22 years of age, showed true menopause, confirmed by circulating levels of pituitary and ovarian hormones and the pattern of vaginal bleeding. Female rhesus monkeys older than 22 years are considered aged, as the maximum average life span for this species is estimated at 30 years [44, 45]. Hence, these females are close to the end of their life span, compared to humans, who are considered as "aged" at around 75 years.

Graham et al. [8] examined the reproductive history and histology of pigtail macaques (*Macaca nemestrina*) by observing females divided into three age classes (4, 10, and 20 years). They reported that one female over 20 years of age showed functional, hormonal, and morphological characteristics of human menopause (i.e., complete follicular depletion, absence of luteal tissue, amenorrhea, increased LH levels, atrophic uterus, and vagina). Miller et al. [56], meanwhile, reported an age-associated decline in fertility in pigtail macaques, similar to the findings for *Macaca sylvanus* reported by Paul et al. [57].

Walker's study [47], of 15 female *Macaca mulatta* aged 8–34 years, was designed to characterize the endocrine and menstrual changes associated with menopause in this species. Findings indicate that females aged 24–26 years were in transition to menopause, evidenced by elevated LH concentrations consistent with a low E_2 concentration and no indication of bleeding menstrual. Also, the histological analysis of their ovaries showed little or no evidence of follicular activity. Finally, the females aged 27–34 years clearly showed a postmenopausal process, marked by high LH concentrations and uniformly low E_2 concentrations. This finding was corroborated by Gilardi et al. [48], who suggest that in female rhesus monkeys menopause does not occur until the second half of the third decade of life. Recent studies have also reported that postmenopausal females show low E_2 and P_4 levels, high indexes of FSH and LH, and a significant decline in the anti-Mullerian hormone and inhibin B. All these findings indicate that these endocrine parameters may be associated with menopause [49]. On the other hand, Johnson and Kapsalis [58] reported a median age >27 years for menopause in free-ranging rhesus monkeys.

Recent studies have concluded that reproductive senescence correlates with overall health [23]. Gore et al. [59], for example, reported that neuroendocrine changes in senescent rhesus monkeys are consistent with those reported in humans [60] and that ovarian changes are related to menopause [61], thus suggesting that these NHPs undergo ovarian changes as a function of aging, similar to humans [40] and chimpanzee [62]. A study of Japanese macaques (*Macaca fuscata*) reported that in free-ranging individuals, fertility rates diminish at around 25 years of age [63], but those normal menstrual cycles continue when they are in captivity, despite a loss of fertility [64]. Finally, recent studies of cynomolgus monkeys (*Macaca fascicularis*) have shown an endocrine pattern similar to that of humans during the postmenopause period [65].

4.2. Great apes

The menstrual cycles, pregnancy, and genital pathology of common chimpanzees (*Pan troglodytes*) were analyzed to determine the extent of perimenopausal changes in females

with aged approximately 35–48 years. However, those analyses showed no clear evidence of menopause, because several females continued cycling until death [8]. But the authors did observe a reduced likelihood of conception in those female chimpanzees, even though they did not "run out" of oocytes before the end of the maximum life span. They concluded that female chimpanzees aged 35 years of age or more show increased reproductive senescence that is quite comparable to what is seen during human climacteric.

Other studies of common chimpanzees aged approximately 48–50 years and of bonobos—pygmy chimpanzees (*Pan paniscus*)—aged approximately 40 years reported that even though the former were extremely aged, they continued to have menstrual cycles and perineal swelling but with increased cycle length. Also, these aged females continue to secrete GnRH in a pulsatile fashion, although the levels of this hormone are higher than younger females [43]. Recent studies by Lacreuse et al. [66] found that many aged chimpanzees continued to menstruate at age 50 or more, but the length of their cycles increased after age 20. Similar results were reported by Videan et al. [67], who concluded that menopause in *Pan troglodytes* occurs at approximately 35–40 years of age. These data concur with the report on wild chimpanzee by Nishida et al. [50]. These authors reported that the females ceased cycling after 30 years of age. On the other hand, Thompson et al. [68] observed that healthy free-ranging chimpanzees remained reproductively viable well past 40 years. They suggested that in *Pan troglodytes*, menopause occurs as a by-product of ill health, interpreting that the onset of menopause may be delayed in relatively healthy, long-lived animals. Studies of female chimpanzees have shown that reproductive aging is similar to that seen in human females, including higher fetal loss as a function of advancing age [69] and the age-related depletion of ovarian follicles [62]. Thus, these studies showed that *Pan troglodyte* females continued cycling into extreme old age, which distinguishes them from human females in terms of menopause.

Other studies in *Pan paniscus* females, aged at least 40 years, showed no external evidence of menstrual cycling preceding death, and hormone levels consistent with clinically observed amenorrhea, but an exaggerated response to the exogenous GnRH challenge. Histological examination of ovaries showed similar characteristics to those described for senile ovarian tissue in humans [43].

Studies of captive orangutan (*Pongo* ssp.) females have reported the endocrine characteristics of their menstrual cycle and similarities to the human cycle [70]. These reports considered births and inter-birth intervals across the life span and demonstrated an age-specific decline in the fertility of captive female orangutans (*Pongo pygmaeus*; [7]). Other studies with wild female Sumatran orangutans (*Pongo abelii*) failed to document menopause, inferred from increased inter-birth intervals in females of estimated age [51]. Interpreting data from wild animals is difficult because of such countervailing factors as female rank, uncertain age, infant mortality, and food availability [1].

An earlier study that described the reproductive physiology of female gorillas (*Gorilla gorilla*) mentioned a correlation of perineal tumescence with circulating hormones and reported a pattern of cyclic hormone secretion similar to that of humans [71]. Recently, fecal hormone determination in two captive female gorillas aged approximately 40 years showed evidence of the protracted luteal phases that are typical of aging human females [72].

Information related to the occurrence of menopause in baboons (*Papio* ssp.) was based on menstrual cycle length, total cessation of cycling that occurs at 26 years of age in captivity [73]. Similar results were reported by Lapin et al. [74], and other studies of wild baboons have reported increased cyclic variability with age and a complete loss of fertility by the age of 25 years. This suggests that baboons undergo age-linked alterations in reproductive function similar to those of humans.

The living conditions of primates have an impact over the animal life span, so the observations in captivity are not always the same as in wild conditions. Although there are some reports about NHP aging process and menopause, they are scarce. Most of the studies report animal physiology and behavior in captivity, because to follow animals in wild by a long period is a very difficult process due to the NHP living conditions.

5. Nonhuman primates as a model to study human being menopause

Due to the biological similarities between human beings and NHPs, the latter have been studied in the search for an adequate model of menopause. However, it is necessary to clearly delimit the similarities and differences among reproductive characteristics, perimenopausal and menopausal changes, and the average life span of different species [1]. Establishing similarities with humans during this search requires considering the characteristics of menopausal processes when animals are in captivity versus those who are free-ranging, in order to avoid the confusions that have led to the assertion that menopause is a uniquely human event [1]. Walker and Herndon [1] suggested that a comparative analysis of female reproductive senescence should focus on the anatomical, physiological, and biochemical changes that are essential to the cessation of ovarian cyclicity, regardless of the presence of menstrual bleeding. There are few reports on menopause in New World primates compared to Old World monkeys, but studies of the latter have observed declines in sexual activity and decreased birth rates. Also, reports on captive apes suggest a long post-reproductive life span, though this has not been confirmed in the wild [30].

Among the different primate taxa, menopause is manifested along an evolutionary continuum: in some species—such as cercopithecines and apes—it is followed by an extended post-reproductive life span, while in others it may presage death. In terms of NHPs as models for menopause, the species that have most often been employed are baboons and chimpanzees. Studies of these primates have attempted to simulate all the consequences that characterize menopause, namely, hormonal and cognitive changes, cardiovascular alterations, and osteoporosis.

Until recently, the occurrence of reproductive termination in NHPs was widely questioned. However, numerous studies have reported that this does indeed occur in several species of Old World monkeys and great apes. Most of this research has been conducted with *Macaca mulatta* [29, 33, 47–49, 59, 61], but other species also experience menopause, including *Pan troglodytes* [43, 62, 67] and *Gorilla gorilla* [27]. For example, the hormonal profiles of peri- and postmenopausal macaques, chimpanzees, and gorillas [1, 61, 67], as well as the age-related decline in the number of primordial follicle in macaques [61] and chimpanzees [62], share many similarities

and occur in a pattern like to that of aging women [40]. On the basis of data from various studies, Fedigan et al. [75] affirmed that "from an endocrinological perspective, reproductive decline may well follow a similar pattern in all primates, and we could use cases of individual post-reproductive monkeys and apes as clinical models of the physiological basis for menopause in human being. However, from an evolutionary perspective, these studies fail to demonstrate similarity between reproductive senescence in NHPs and menopause in the human female. Instead, they highlight the critical differences: female macaques and chimpanzees that cease to cycle very close to age at death, whereas human females cease to cycle in middle age; female macaques and chimpanzees cease to cycle on an idiosyncratic basis, whereas human females universally cease to cycle at the average age of approximately 50 years."

In light of these data, it is clear that regardless of the age at the onset of menopause, there are numerous physiological similarities between the females of NHPs and human females with respect to the gradual decline and eventual cessation of reproductive capacity. For this reason, several authors of excellent reviews [1, 29, 30] have proposed that NHPs provide the most appropriate animal models available for analyzing menopause in human females and the processes associated with it.

Although NHPs present a rich opportunity to study the process of reproductive senescence or menopause (i.e., the permanent, non-pathological, age-associated cessation of ovulation, [1]) and play a unique role in translational science by bridging the gap between basic and clinical research [76], their use as experimental subjects is limited by the lack of available NHPs that are undergoing the perimenopausal transition and natural menopause, their short menopausal compared to that of human being, high costs, and the strict ethical guidelines that researchers must follow when studying them (see Ref. [33, 76]).

Despite these difficulties, the use of NHPs as study models has several advantages. Macaques (*Macaca* spp.), including *Macaca mulatta* and *Macaca fascicularis* monkeys, for example, have been particularly useful due to their availability, moderate size, and ability to adapt to laboratory conditions. Also, approximately 95% of the overall genetic coding sequence of macaques is identical to that of humans [77], and many of their physiological systems are comparable. Finally, because they are relatively long lived, they are effective models for studying a number of diseases and conditions that increase in frequency with aging. These factors explain why female macaques have been the preferred model for examining critical health concerns of human beings, including luteal phase deficiencies and hypothalamic amenorrhea [78], obesity and diabetes [79], cardiovascular diseases [80], osteopenia, osteoporosis [81], osteoarthritis [82], cognitive deficits associated with age [76], and—at least potentially—decreased interest in mating [83].

If a single conclusion can be gleaned from this brief summary, it is that a large number of physiological conditions and pathologies that human beings experience during their lifetime appear to be broadly manifested in primate taxa, though information is lacking in other regards, such as the interaction between deficits in cognitive processes and their effect on the modulation of social and sexual interaction.

Primates are mammals distinguished by their large brains, advanced cognitive abilities, flexible behavior, and sophisticated social systems [84]. For example, chimpanzees have the ability

to recognize themselves in a mirror [85] and perform tasks involving concept formation [86]. Moreover, the structure and function of human and NHP brains are very similar. In this regard, we can mention nuclear organization, projection pathways, and innervation patterns [87], as well as similar cortical development and organization [88], including visual cortical functional divisions and prefrontal cortex subdivisions [89] that are critical for cognitive processes [90].

In human beings and NHPs, cognitive and reproductive functions decline gradually with advancing age and more precipitously with the loss of circulating estrogen that occurs during menopause. Cognitive deficits in NHPs can be quantified over their life span using a battery of cognitive tests that are similar to, if not the same as, those used with humans [91]. These include the monkey version of the Wisconsin Card Sorting Test (WCST) [92], which is the gold standard for assessing cognitive flexibility in humans. Using a version of WCST (without the numerosity category), executive function deficits have been reported in both middle-aged and older rhesus monkeys [93], as well as in middle-aged menopausal rhesus monkeys [91]. However, the limited availability of animals of adequate age [33] means that studies with monkeys typically involve only a few animals and use premenopausal ovariectomized subjects rather than naturally menopausal females.

Given the dramatic effects of sex steroids on neuronal morphology and brain activity in regions involved in cognition, one might expect that age-related changes in the endocrine milieu will have important consequences for cognitive functions. In effect, data on aged, naturally or surgically menopausal monkeys indicate that estrogen does indeed modulate a broad range of cognitive domains, such as learning and memory. These effects observed appear to be task specific and sensitive to the time that passed without estrogen prior to estrogen replacement. For example, on the delayed response (DR) task—a test of prefrontal functioning—it was noted that performance was impaired in postmenopausal individuals compared to age-matched premenopausal rhesus monkeys [94]. This result suggests that the absence of estrogen, associated with menopause, could be detrimental to prefrontal functioning.

Although the effects of the menstrual cycle, estrogen withdrawal, and estrogen replacement in young monkeys appear limited to non-mnemonic functions, such as attention or aspects of face processing [95], a broad range of cognitive functions, including memory, are sensitive to estrogen deprivation and replacement in older monkeys [92]. Neurobiological data are consistent with such cognitive findings and demonstrate an array of morphological and physiological changes following ovariectomy and/or estrogen replacement in brain areas that are important for cognition.

Although the specific mechanisms through which estrogens may affect cognition remain to be elucidated, it is clear that these hormones have broad effects on areas of the brain that play key roles in cognitive functions [96]. Estrogen receptors are found in the cerebral cortex, hippocampus, and amygdala in both monkeys [97] and human beings [98]. Estrogens alter the neuronal morphology and physiology of some of these areas [99].

NHPs provide valuable animal models that have significantly advanced our understanding of numerous behavioral and biological phenomena in humans and other primates. Their value

as models for studying menopause in humans derives from their common ancestry, as well as a series of hormonal, cognitive, and social influences that are similar to those experienced by human beings. The aging process or menopause has been also explored focusing through the neural basis of cognitive functioning, revealing not only alterations over specific neural systems but also differences in the affectation level among brain regions and neurobiological parameters. Therefore, further research into the interactions among hormones and various neurotransmitter systems could potentially produce improved knowledge of the neural and hormonal bases that comprehend the gamma of alterations that human beings suffer before, during, and after menopause.

5.1. Anxiety and depression during natural or surgical menopause of nonhuman primates

The decrease in ovarian hormones during natural and surgical menopause is associated with a higher incidence of psychiatric disorders, such as anxiety and depression in vulnerable women, where the decrease of hormones—principally E_2 and P_4—can induce neural changes that exert affects on both the emotional and affective levels [100]. In this regard, ovariectomies in NHPs have been used as a model of surgical menopause at the experimental level, given that the absence of certain hormones induced by ovariectomy can reproduce the physiological, emotional, and affective change characteristic of menopause.

At the behavioral level, ovariectomized primates may exhibit anxiety and depression-related behaviors. For example, long-term ovariectomy may increase anxiety in Japanese macaques (*Macaca fuscata*), associated with decreases in such behaviors as positive social contact, dominance, and the time spent receiving grooming. Similarly, temperament tests performed on these individuals show an increase in anxiogenic behavior [101]. Furthermore, ovariectomized pigtail macaques (*Macaca nemestrina*) present higher scratching rates [102], a well-established indicator of anxiety in NHPs, while in Japanese macaques, a reduction in locomotion has been observed after ovariectomy [101], in association with depressive behavior. Therefore, these behavioral alterations are probably due to the absence of ovarian hormones, given that after ovariectomy in rhesus (*Macaca mulatta*) and pigtail macaques a reduction in E_2 and P_4 concentrations is detected, in relation to increased anxiety [102].

The absence of ovarian hormones in NHPs may also generate neural changes in the brain (**Table 1**). Studies of ovariectomized Japanese monkeys have detected downregulation of estrogen receptor beta (ER-β) in the subiculum of hippocampal formation, while postmenopausal monkeys of the same species have shown upregulation of ER-β [103]. On the other hand, in ovariectomized African green monkeys (*Cercopithecus aethiops sabaeus*), a reduction of synaptic plasticity of the hippocampus was detected [104]. Given that the reduced density of dendritic spines and ER-β in the hippocampus is related to an increase in indicators of anxiety and depression in ovariectomized rodents [105], this is probably occurring as well in nonhuman primates that experience surgical menopause. In addition, the long-term absence of ovarian hormones may impact serotonergic activity. For example, it has been demonstrated that ovariectomy in rhesus macaques reduces expression of the mRNA of the tryptophan

Species	Natural menopause/ ovariectomy	Neural changes	Related behavior	References
African green monkeys (*Cercopithecus aethiops sabaeus*)	Ovariectomy	Reduced density of dendritic spines in the CA1 layer of the hippocampus	Not reported	[104]
Pigtail macaques (*Macaca nemestrina*)	Ovariectomy	Not reported	Anxiety	[102]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Increased expression of MAO-A protein and decreased expression of TPH and SERT proteins in the dorsal raphe nucleus	Not reported	[107]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Decreased expression of TPH2 mRNA in the dorsal raphe nucleus	Not reported	[108]
Rhesus macaques (*Macaca mulatta*)	Ovariectomy	Increased DNA fragmentation of serotonin neurons in the dorsal raphe nucleus	Not reported	[106]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Not reported	Anxiety and depression	[101]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Reduced Fev, TPH-2, SERT, and $5HT_{1A}$ gene expression in the dorsal raphe nucleus	Not reported	[109]
Japanese macaques (*Macaca fuscata*)	Natural menopause	Upregulation in the ER-β immunoreactivity in the subiculum of the hippocampal formation	Not reported	[103]
Japanese macaques (*Macaca fuscata*)	Ovariectomy	Downregulation in the ER-β immunoreactivity in the subiculum of the hippocampal formation	Not reported	[103]

Table 1. Neural changes related to anxiety and depressive-like behaviors in nonhuman primates with natural or surgical menopause.

hydroxylase-2 (TPH-2) enzyme, increases the expression of MAO-A, and increases DNA fragmentation of serotonin neurons in the dorsal raphe nucleus [106]. These events could lead, on the one hand, to greater serotonin degradation and, on the other, neuronal death and, finally, a malfunction of the serotonergic system.

Furthermore, long-term ovariectomy in Japanese macaques reduces the expression of serotonergic neurons and gene expression of TPH-2, the serotonin reuptake transporter (SERT), and $5HT_{1A}$ autoreceptors in the dorsal raphe nucleus [109]. This agrees with data showing that in depressed female of *Macaca fascicularis* the binding potential of $5HT_{1A}$ receptors is reduced in the hippocampus, amygdala, and cingulate cortex [110], three of the structures involved in the pathophysiology of anxiety and depression. In contrast, stress-sensitive female monkeys of the same species decrease levels of Fev (transcription factor that determines whether a neuron is serotonergic),

TPH-2, SERT, and $5HT_{1A}$ mRNAs in the dorsal raphe nucleus [111]. Thus, in the long term, the reduction of TPH-2, which is important for serotonin synthesis, together with determinant markers for serotonergic function, could generate a higher incidence of anxious and depressive behaviors in NHPs with menopause, as occurred in human beings.

On the other hand, exogenous administration of E_2 or P_4 in ovariectomized primates has the capacity to restore serotonergic neurotransmission [106]. Further, serotonin neurons can express the ER-β protein and ER-β mRNA [112]. And, therefore, estrogens could increase the availability of serotonin in the brain by interacting with its receptor. Thus, the absence of ovarian hormones, such as E_2 and P_4, has the ability to induce changes at the level of the the central nervous system in primates [103]. This evidence suggests that neural changes could be related to anxiety and depression behaviors, which could indicate some vulnerability in NHPs that experience natural or surgical menopause or suffer changes in different neurotransmission systems in which ovarian hormones participate, all of which could affect the emotional and affective state of these individuals.

6. Conclusion

Menopause is a natural process that entails the permanent cessation of ovulation. It is associated with physiological and structural changes in aging females. Although it has long been assumed that menopause occurs only in human beings, the search for medical/clinical models to aid in research on this process has revealed that some species of NHPs also exhibit menopause. However, certain differences between human females and NHPs are clear: shorter postmenopausal life spans and variations in the timing of hormonal changes during the menopausal transition. But NHP models allow us to better understand not only several of the processes that occur during human aging—such as cognitive changes, cardiovascular alterations, and osteoporosis—but also similarities among species along the taxonomic scale.

On the other hand, increases in anxiety and depression behaviors may be observed in NHPs that undergo natural or surgical menopause. In a comparative perspective, these findings could improve our understanding of the neurobiological mechanisms that underlie emotional and affective disorders associated with the absence of ovarian hormones, given that experiments have demonstrated that long-term hormonal absence has the ability to affect numerous neurotransmission systems involved in mood disorders. In addition to reproducing various neural changes that can be correlated with depressive and anxious behaviors in NHPs, this might help understand the neurobiological substrate of emotional and affective disorders that can appear in women who experience natural or surgical menopause.

Acknowledgements

The authors of the present chapter received support from the following institutions: Sistema Nacional de Investigadores, SNI 60372-0 (AAA-T); Consejo Nacional de Ciencia y Tecnología (CONACyT), 297410 (AP-O); and Universidad Veracruzana, 46392 (BPV-D).

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References

[1] Walker ML, Herndon JG. Menopause in nonhuman primates?. Biology of Reproduction. 2008;**79**:398-406. DOI: 10.1095/biolreprod.108.068536

[2] Rance N. Menopause and the human hypothalamus: Evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen. Peptides. 2009;**30**:111-122. DOI: 10.1016/j.peptides.2008.05.016

[3] Hall J. Neuroendocrine changes with reproductive aging in women. Seminars in Reproductive Medicine. 2007;**25**:344-351. DOI: 10.1055/s-2007-984740

[4] Wilson EO. The Relevant Principles of Population Biology: Sociobiology. Cambridge: The Belknap Press; 1975. pp. 32-47

[5] Hill K, Hurtado A. Ache life history: The ecology and demography of a foraging people. American Ethonologist. 1996;**26**:531-532. DOI: 10.1525/ae.1999.26.2.531

[6] Pavelka M, Fedigan L. Reproductive termination in female Japanese monkeys: A comparative life history perspective. American Journal of Physical Anthropology. 1999;**109**: 455-464

[7] Caro TM, Sellen DW, Parish A, Frank R, Brown DM, Voland E, Borgerhoff Mulder M. Termination of reproduction in nonhuman and human primate females. International Journal of Primatology. 1995;**16**:205-220. DOI: 10.1007/BF02735478

[8] Graham CE, Kling OR, Steiner RA. Reproductive senescence in female nonhuman primates. In: Bowden DM, editor. Aging in Nonhuman Primates. New York: Van Nostrand Reinhold; 1979. 183-202

[9] Scott P. Menopause: Adaptation or epiphenomenon?. Evolutionary Anthropology. 2001; **10**:43-57. DOI: 10.1002/evan.1013

[10] Fleagle J. Apes and humans. In: Fleagle J, editor. Primate Adaptation and Evolution. 3rd ed. New York, Elsevier; 2013. Pp. 151-168. DOI: 10.1016/B978-0-12-378632-6.0007-0

[11] DuMond FV. The Squirrel Monkey in a Seminatural Environment. New York: Academic Press; 1968

[12] Keverne E. Do Old World primates have oestrus. Malaysian Applied Biology. 1981;**10**: 119-126

[13] Hrdy SB, Whitten P. Patterning of sexual activity. In: Smuts BB, Cheney DL, Seyfarth RM, Wrangham RW, Struhsaker TT, editors. Primates Societies. Chicago and London, University of Chicago Press; 1986; **30**:359-370

[14] Dixson AF. Primate Sexuality: Comparative Studies of the Prosimians, Monkeys, Apes, and Human Beings. Trends in Ecology and Evolution. Inglaterra: Oxford University Press; 1998

[15] Ziegler T, Strier K, Van S. The reproductive ecology of South American primates: Ecological adaptations in ovulation and conception. In: Garber PA, Estrada A, Bicca-Marques JC, Heymann EW, Strier KB, editors. South American Primates: Comparative Perspectives in the Study of Behavior, Ecology, and Conservation. New York: Springer; 2009. pp. 191-210 . DOI: 10.1007/978-0-387-78705-3_8

[16] Yen SC, Jaffe RB. Reproductive Endocrinology: Physiology, Pathophysiology and Clinical Management. Philadelphia: Saunders Company; 1986

[17] Zeleznik AJ, Pohl CR. Control of Follicular development, Corpus Luteum function, the maternal recognition of pregnancy, and the Neuroendocrine regulation of the menstrual cycle in higher primates. Academic Press. 2006; **45**:2449-2510. DOI: 10.1016/b978-012515400-0/50050-6

[18] Bonello N, Jasper MJ, Norman RJ. Periovulatory expression of intercellular adhesion molecule-1 in the rat ovary. Biology Reproduction. 2004;**71**:1384-1390. DOI: 10.1095/biolreprod.104.030650

[19] Hodgen GD, Itskovitz J. Recognition and maintenance of pregnancy. In: Knobil E, Neill J, editors. The Physiology of Reproduction. New York: Raven Press; 1988

[20] Saltzman W, Tardif S, Rutherford J. Hormones and reproductive cycles in primates. In: Hormones and Reproduction of Vertebrates. United States of America, Elsevier Inc. 2011;**5**:291-327. DOI: 10.1016/B978-0-12-374928-4.10013-6

[21] Martin RD. The evolution of human reproduction: A primatological perspective. American Journal of Physical Anthropology. 2007;**50**:59-84. DOI: 10.1002/ajpa.20734

[22] Johnson MH. Everitt B. Essential Reproduction. Oxford, OXF, Inglaterra: Blackwell Science; 2000

[23] Thompson ME. The endocrinology of intersexual relationships in the apes. In Thorpe P, Grey P, editors. The Endocrinology of Social Relationships. Cambridge: Harvard University Press; 2009. pp. 196-222

[24] Dukelow W. Reproductive cyclicity and breeding in the squirrel monkey. In: Rosenblum LA, Coe CL, editors. Handbook of Squirrel Monkey Research. NY: Plenum Press; 1985. pp. 169-190 . DOI: 10.1007/978-1-4757-0812-7_7

[25] Strassmann BI The evolution of endometrial cycles and menstruation. The Quarterly Reviex of Biology. 1996;**71**:181-220. DOI: 10.1086/419369

[26] Gangestad SW, Thornhill R. Human oestrus. Proceeding of the Royal Society B. 2008;**275**:991-1000. DOI: 10.1098/rspb.2007.1425

[27] Atsalis S, Margulis SW. Perimenopause and menopause: Documenting life changes in aging female gorillas. In: Atsalis S, Margulis SW, Hof PR, editors. Primate Reproductive Aging. Switzerland: Kargel AC; 2008. pp. 119-146 . DOI: 10.1159/000137704

[28] Wise PM. Aging of the female reproductive system. In: Masoro EJ, Austad SN, editors. Handbook of the Biology of Aging. London: Elsevier; 2006. pp. 570-590 . DOI: 10.1016/B978-012088387-5/50024-8

[29] Hodgen G, Goodman A, O'Connor A, Johnson D. Menopause in rhesus monkeys: Model for study of disorders in the human climacteric. American Journal of Obstetrics Gynecology. 1977;**127**:581-584. DOI: 10.1016/0002-9378(77)90352-0

[30] Atsalis S, Margulis SW. Primate reproductive aging: From lemurs to humans. In: Atsalis S, Marguli S, Hof P, editors. Primate Reproductive Aging. Switzerland: Kargel AC. 2008. pp. 186-194 . DOI: 10.1159/000137710

[31] Wright P, King S, Baden A, Jernvall J. Aging in wild female lemurs: Sustained fertility with increased infant mortality. In: Primate Reproductive Aging. Vol. **36**. Chicago, New York, Karger Publishers; 2008. pp. 17-28 . DOI: 10.1159/000137677

[32] Vom Saal FS, Finch CE. Reproductive senescence: Phenomena and mechanisms in mammals and selected vertebrates. In: Knobil E, Neill J, editors. The Physiology of Reproduction. New York: Raven Press; 1988. pp. 2351-2413

[33] Bellino FL, Wise PM. Nonhuman primate models of menopause workshop. Biology of Reproduction. 2003;**68**:10-18. DOI: 10.1095/biolreprod.102.005215

[34] Hawkes K, O'Connell JF, Blurton Jones NG, Alvarez H, Charnov EL. Grandmothering, menopause, and the evolution of human life histories. Proceedings of the National Academy of Sciences. 1998:**95**:1336-1339

[35] Hansen K, Knowlton N, Thyer A, Charleston J, Soules M, Klein N. A new model of reproductive aging: The decline in ovarian non-growing follicle number from birth to menopause. Human Reproduction. 2008;**23**:599-708. DOI: 10.1093/humrep/dem408

[36] Soules M, Sherman S, Parrot E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric. 2001;**4**:267-272. DOI: 10.1080/cmt.4.4.267.272

[37] Van Noord-Zaadstra B, Looman C, Alsbach H, Habbema J, te Velde E, Karbaat J. Delayed childbearing: Effect of age on fecundity and outcome of pregnancy. British Medical Journal. 1991;**302**:1361-1365

[38] Hansen K, Thyer A, Sluss P, Bremner W, Soules M, Klein N. Reproductive ageing and ovarian function: Is the early follicular phase FSH rise necessary to maintain adequate secretory function in older ovulatory women? Human Reproduction. 2005;**20**:89-95. DOI: 10.1093/humrep/deh54

[39] Klein NA, Harper AJ, Houmard BS, Sluss P, Soules M. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? The Journal of Clinical Endocrinology and Metabolism. 2002;**87**:5746-5750. DOI: 10.1210/jc.2002-020622

[40] Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: Evidence for accelerated loss and ultimate exhaustion. The Journal of Clinical Endocrinology & Metabolism. 1987;**65**:1231-1237. DOI: 10.1210/jcem-65-6-1231

[41] Gosden RG. Biology of Menopause: The Cause and Consequence of Ovarian Ageing. London: Academic Press; 1985

[42] Waser P. Postreproductive survival and behavior in a free-ranging female mangabey. Folia Primatologica. 1978;**29**:142-160. DOI: 10.1159/000155836

[43] Gould K, Flint M, Graham C. Chimpanzee reproductive senescence: A possible model for evolution of the menopause. Maturitas. 1981;**3**:157-166. DOI: 10.1016/0378-5122(81)90007-4

[44] Van Wagenen G. Menopause in subhuman primate. The Anatomical Record. 1970;**166**:392.

[45] Tigges J, Gordon TP, McClure HM, Hall EC, Peters A. Survival rate and life span of rhesus monkeys at the Yerkes Regional Primate Center. American Journal Primatology. 1988;**15**:263-273 DOI: 10.1002/ajp.1350150308

[46] Zapantis G, Santoro N. The menopausal transition: Characteristics and management. Best Practice and Research: Clinical Endocrinology and Metabolism. 2003;17:33-52 DOI: 10.1016/S1521-690X(02)00081-7

[47] Walker ML. Menopause in female rhesus monkeys. American Journal of Primatology. 1995;**35**:59-71. DOI: 10.1002/ajp.1350350106

[48] Gilardi KVK, Shideler SE, Valverde CR, Roberts JA, Lasley BL. Characterization of the onset of menopause in the rhesus macaque. Biology of Reproduction. 1997;**57**:335-340. DOI: 10.1095/biolreprod57.2.335

[49] Downs JL, Urbanski HF. Neuroendocrine changes in the aging reproductive axis of female rhesus macaques (*Macaca mulatta*). Biology of Reproduction. 2006:**75**:539-546. DOI: 10.1095/biolreprod.106.051839

[50] Nishida T, Corp N, Hamai M, Hasegawa Y, Hiraiwa-Hasegawa M, Hosaka K, et al. Demography, female life history, and reproductive profiles among the chimpanzees of Mahale. American Journal Primatology. 2003;**59**:99-121. DOI: 10.1002/ajp.10068

[51] Wich SA, Utami-Atmoko SS, Setia TM, Rijksen HD, Schürmann C, van Hooff JA, et al. Life history of wild Sumatran orangutans (*Pongo abelii*). Journal Human Evolution. 2004;**47**:385-398. DOI: 10.1016/j.jhevol.2004.08.006

[52] Hamilton WD III, Busse C, Smith KS. Adoption of infant orphan chacma baboons. Animal Behavior. 1982;**30**:29-34. DOI: 10.1016/S0003-3472(82)80233-9

[53] Teleki G, Hunt EE, Pfifferling JH. Demographic observations (1963-1973) on the chimpanzees of Gombe National Park, Tanzania. Journal of Human Evolution. 1976;**5**:559-598. DOI: 10.1016/0047-2484(76)90004-X

[54] Van Noordwijk MA, Van Schaik CP. Development of ecological competence in *Sumatran orangutans*. American Journal Physical Anthropology. 2005;**127**:79-94. DOI: 10.1002/ajpa.10426

[55] Machatschke IH, Wallner B, Dittami J. Impact of social environment on female chimpanzee reproductive cycles. Hormones and Behavior. 2006;**50**:126-131. DOI: 10.1016/j.yhbeh.2006.02.003

[56] Miller PB, Charleston JS, Battaglia DE, Klein NA, Soules MR. Morphometric analysis of primordial follicle number in pigtailed monkey ovaries: Symmetry and relationship with age. Biology of Reproduction. 1999;**61**:553-556

[57] Paul A, Kuester J, Podzuweit D. Reproductive senescence and terminal investment in female Barbary macaques (*Macaca sylvanus*) at Salem. International Journal of Primatology. 1993;**14**:105-124. DOI: 10.1007/BF02196506

[58] Johnson R, Kapsalis E. Menopause in free-ranging rhesus macaques: Estimated incidence, relation to body condition and adaptive significance. International Journal of Primatology. 1998;**19**:751-765. DOI: 10.1023/A:1020333110918.

[59] Gore AC, Windsor-Engnell BM, Terasawa E. Menopausal increases in pulsatile gonadotropin-releasing hormone release in a nonhuman primate (*Macaca mulatta*). Endocrinology. 2004;**145**:4653-4659. DOI: 10.1210/en.2004-0379

[60] Gill S, Sharpless JL, Rado K, Hall JE. Evidence that GnRH decreases with gonadal steroid feedback but increases with age in postmenopausal women. Journal of Clinical Endocrinology and Metabolins. 2002;**87**:2290-2296. DOI: 10.1210/jcem.87.5.8508

[61] Nichols SM, Bavister BD, Brenner CA, Didier, PJ, Harrison R, Kubisch, HM. Ovarian senescence in the rhesus monkey (*Macaca mulatta*). Human Reproduction. 2005;**20**:79-83. DOI: 10.1093/humrep/deh576

[62] Jones KP, Walker LC, Anderson D, Lacreuse A, Robson SL, Hawkes K. Depletion of ovarian follicles with age in chimpanzees: Similarities to humans. Biology of Reproduction. 2007;**77**:247-251. DOI: 10.1095/biolreprod.106.059634

[63] Itogawa N, Tanaka T, Ukai N, Fujii H, Kurokawa T, Ando A, Watanabe Y, Imakawa S. Demography and reproductive parameters of a free-ranging group of Japanese macaques (*Macaca fuscata*) at Katsuyama. Primates. 1992;**33**:49-68. DOI: 10.1007/BF02382762

[64] Nozaki M, Mitsunaga F, Shimizu K. Reproductive senescence in female Japanese monkeys (*Macaca fuscata*): Age- and season-related changes in hypothalamic-pituitary-ovarian functions and fecundity rates. Biology of Reproduction. 1995;**52**:1250-1257

[65] Kavanagh K, Koudy Williams J, Wagner JD. Naturally occurring menopause in cynomolgus monkeys: Changes in hormone, lipid, and carbohydrate measures with hormonal status. Journal of Medical Primatology. 2005;**34**:171-177. DOI: 10.1111/j.1600-0684.2005.00114.x

[66] Lacreuse A, Chennareddi L, Johnson J, Gould KG, Hawkes K, Wijayawardana S, et al. Menstrual cycles continue into advanced old age in the common chimpanzee (*Pan troglodytes*). Biology of Reproduction. 2008;**79**:407-412. DOI: 10.1095/biolreprod.108.068494.

[67] Videan E, Fritz J, Heward C, Murphy J. The effects of aging on hormone and reproductive cycles in female chimpanzees (*Pan troglodytes*). Comparative Medicine. 2006;**56**:291-299.

[68] Thompson ME, Jones JH, Pusey AE, Brewer-Marsden S, Goodall J, Marsden D, et al. Aging and fertility patterns in wild chimpanzees provide insights into the evolution of menopause. Current Biology. 2007;**17**(24):2150-2156. DOI: 10.1016/j.cub.2007.11.033

[69] Holman DJ, Wood JW. Pregnancy loss and fecundity in women. In: Ellison PT, editor. Reproduction, Ecology, and Human Evolution. New York: Aldine de Gruyter; 2001. pp. 15-38

[70] Collins DC, Graham CE, Preedy JR. Identification and measurement of urinary estrone, estradiol-17-beta, estriol, pregnanediol and androsterone during the menstrual cycle of the orangutan. Endocrinology. 1975;**96**:93-101. DOI: 10.1210/endo-96-1-93

[71] Nadler RD. Reproductive physiology and behavior of gorillas. Journal of Reproduction and Fertility. 1980;(Suppl 28):79-89

[72] Margulis SW, Atsalis S, Bellem A, Wielebnowski N. Assessment of reproductive behavior and hormonal cycles in geriatric western Lowland gorillas. Zoo Biology. 2007;**26**:117-139. DOI: 10.1002/zoo.20124

[73] Martin LJ, Carey KD, Comuzzie AG. Variations in menstrual cycle length and cessation of menstruation in captive raised baboons. Mechanisms of Ageing and Development. 2003;**124**:865-871. DOI: 10.1016/S0047-6374(03)00134-9

[74] Lapin BA, Krilova RI, Cherkovich GM, Asanov NS. Observations from Sukhumi. In: Bowden DB, editor, Aging in Nonhuman Primates. New York: Van Nostrand Reinhold; 1979. pp. 14-37

[75] Fedigan LM, Pavelka MSM Campbell C, Fuentes A, MacKinnon KC, Panger M, et al. Reproductive cessation in female primates comparisons of Japanese macaques and humans. In: Campbell C, Fuentes A, MacKinnon K, Panger M, Bearder S, editors. Primates in Perspective. United Kingdom, Oxford University Press; 2006. pp. 437-447

[76] Shively CA, Clarkson TB. The unique value of primate models in translational research. American Journal of Primatology. 2009;**71**:715-721. DOI: 10.1002/ajp.20720

[77] Magness CL, Fellin PC, Thomas M, Korth M, Agy M, Proll, S, et al. Analysis of the *Macaca mulatta* transcriptome and the sequence divergence between *Macaca* and human. Genome Biology. 2005;**6**:60. DOI: 10.1186/gb-2005-6-7-r60

[78] Kaplan JR, Manuck SB. Ovarian dysfunction, stress, and disease: A primate continuum. ILAR Journal. 2004; **45**:89-115. DOI: 10.1093/ilar.45.2.89

[79] Wagner JD, Kavanagh K, Ward GM, Auerbach BJ, Harwood H, Kaplan JR. Old world nonhuman primate models of type 2 diabetes mellitus. ILAR Journal. 2006;**47**:259-271. DOI: 10.1093/ilar.47.3.259

[80] Shively CA, Kaplan JR, Clarkson T. Carotid artery atherosclerosis in cholesterol-fed cynomolgus monkeys: The effects of oral contraceptive treatments, social factors and regional adiposity. Arteriosclerosis Thrombosis and Vascular Biology. 1990;**10**:358-366. DOI: 10.1161/01.ATV.10.3.358

[81] Jerome CP, Peterson PE. Nonhuman primate models in skeletal research. Bone. 2001;**29**:1-6. DOI: 10.1016/S8756-3282(01)00477-X

[82] Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP. Osteoarthritis in cynomolgus macaques. III: Effects of age, gender, and subchondral bone thickness on the severity of disease. Journal of Bone and Mineral Research. 1996;**11**:1209-1217. DOI: 10.1002/jbmr.5650110904

[83] Wallen K. Sex and context: Hormones and primate sexual motivation. Hormones and Behavior. 2001;**40**:339-357. DOI: 10.1006/hbeh.2001.1696

[84] Hartwig W. Primate evolution and Taxonomy. In: Campbell C, Fuentes A, MacKinnon, K, Bearder S Stumpf R, editors. Primates in Perspective. 2nd ed. New York: Oxford University Press. 2007. pp. 11-22

[85] Povinelli DJ, Rulf AB, Landau KR, Bierschwale DT. Self-recognition in chimpanzees (*Pan troglodytes*): Distribution, ontogeny, and patterns of emergence. Journal of Comparative Psychology. 1993;**107**(4):347

[86] Thompson R, Oden DL. Categorical perception and conceptual judgements by nonhuman primates: The paleological monkey and the analogical ape. Cognitive Science. 2000;**24**:363-396. DOI: 10.1016/S0364-0213(00)00029-X

[87] Amaral D, Lavenex P. Hippocampal neuroanatomy. In: Anderson P, Morris R, Amaral D, Bliss T, O'Keefe J, editors. The Hippocampus Book. New York: Oxford University Press; 2009. DOI: 10.1093/acprof:oso/9780195100273.003.0003.

[88] Hutchison RM, Everling S. Monkey in the middle: Why non-human primates are needed to bridge the gap in resting-state investigations. Frontiers in Neuroanatomy. 2012;**6**:1-19. DOI: 10.3389/fnana.2012.00029

[89] Uylings HBM, Groenewegen HJ, Kolb B. Do rats have a prefrontal cortex?. Behavioural Brain Research. 2003;**146**:3-17. DOI: 10.1016/j.bbr.2003.09.028

[90] Phillips K, Bales K, Capitanio J, Conley A, Czoty P, t Hart B, et al. Why primate models matter. American Journal of Primatology. 2014;**76**:801-827. DOI: 10.1002/ajp.22281

[91] Voytko M, Tinkler G. Cognitive function and its neural mechanisms in nonhuman primate models of aging, Alzheimer disease, and menopause. Frontiers in Bioscience. 2004;**9**:1899-1914. DOI: 10.2741/1370

[92] Lacreuse A, Chhabra R, Hall M, Herndon J. Executive function is less sensitive to estradiol than spatial memory: Performance on an analog of the card sorting test in ovariectomized aged rhesus monkeys. Behavioural Processes. 2004;**67**:313-319. DOI: 10.1016/j.beproc.2004.05.004

[93] Moore TL, Killiany RJ, Herndon JG, Rosene DL. Moss M. Executive system dysfunction occurs as early as middle-age in the rhesus monkey. Neurobiology of Aging. 2006;**27**:1484-1493. DOI: 10.1016/j.neurobiolaging.2006.08.004

[94] Roberts JA, Gilardi K, Lasley B, Rapp PR. Reproductive senescence predicts cognitive decline in aged female monkeys. Neuroreport. 1997;**8**:2047-2051

[95] Landauer N, Kohama SG, Voytko ML, Neuringer M. Effects of menstrual cycle status on visuospatial attention in aged rhesus monkeys. Society for Neuroscience Abstract. 2004;**34**:779-782

[96] McEwen BS, Alves SE. Estrogen actions in the central nervous system 1. Endocrine Reviews. 1999;**20**:279-307. DOI: 10.1210/edrv.20.3.0365

[97] Gundlah C, Kohama SG, Mirkes SJ, Garyfallou VT, Urbanski HF, Bethea C. Distribution of estrogen receptor beta (ERbeta) mRNA in hypothalamus, midbrain and temporal lobe of spayed macaque: Continued expression with hormone replacement. Molecular Brain Research. 2000;**76**:191-204. DOI: 10.1016/S0006-8993(99)02475-0

[98] Osterlund M, Gustafsson JA, Keller E, Hurd YL. Estrogen receptor beta (ERbeta) messenger ribonucleic acid (mRNA) expression within the human forebrain: Distinct distribution pattern to ERalpha mRNA. The Journal of Clinical Endocrinology & Metabolism. 2000;**85**:3840-3846. DOI: 10.1210/jcem.85.10.6913

[99] Tang Y, Janssen WGM, Hao J, Roberts JA, McKay H, Lasley B, et al. Estrogen replacement increases spinophilin-immunoreactive spine number in the prefrontal cortex of female rhesus monkeys. Cerebral Cortex. 2004;**14**:215-223. DOI: 10.1093/cercor/bhg121

[100] Rodríguez-Landa JF, Puga-Olguín A, Germán-Ponciano LJ, García-Ríos RI, Soria-Fregozo C. Anxiety in natural and surgical menopause—Physiologic and therapeutic bases. In: Durbano F, editor. A Fresh Look at Anxiety Disorders. Rijeka: InTech; 2015. pp. 173-198 . DOI: 10.5772/60621

[101] Coleman K, Robertson ND, Bethea CL. Long-term ovariectomy alters social and anxious behaviors in semi-free ranging Japanese Macaques. Behavioural Brain Research. 2011;**225**:317-327. DOI: 10.1016/j.bbr.2011.07.046

[102] Pazol K, Wilson ME, Wallen K. Medroxyprogesterone acetate antagonizes the effects of estrogen treatment on social and sexual behavior in female macaques. Journal of Clinical Endocrinology & Metabolism. 2004;**89**:2998-3006. DOI: 10.1210/jc.2003-032086

[103] Higaki S, Takumi K, Itoh M, Watanabe G, Taya K, Shimizu K, Hayashi M, Oishi T. Response of ERβ and aromatase expression in the monkey hippocampal formation to ovariectomy and menopause. Neuroscience Research. 2012;**72**:148-154. DOI: 10.1016/j.neures.2011.10.007

[104] Leranth C, Shanabrough M, Redmond D. Gonadal hormones are responsible for maintaining the integrity of spine synapses in the CA1 hippocampal subfield of female nonhuman primates. Journal of Comparative Neurology. 2002;**447**:34-42. DOI: 10.1002/cne.10230

[105] Velázquez-Zamora DA, González-Tapia D, González-Ramírez MM, Flores-Soto ME, Vázquez-Valls E, Cervantes M, González-Burgos I. Plastic changes in dendritic spines of hippocampal CA1 pyramidal neurons from ovariectomized rats after estradiol treatment. Brain Research. 2012;**1470**:1-10. DOI: 10.1016/j.brainres.2012.06.012

[106] Lima FB, Bethea CL. Ovarian steroids decrease DNA fragmentation in the serotonin neurons of non-injured rhesus macaques. Molecular Psychiatry. 2010;**15**:657-668. DOI: 10.1038/mp.2009.97

[107] Smith LJ, Henderson JA, Abell CW, Bethea CL. Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of Macaques. Neuropsychopharmacology. 2004;**29**:2035-2045. DOI: 10.1038/sj.npp.1300510

[108] Sanchez RL, Reddy AP, Centeno ML, Henderson JA, Bethea CL. A second tryptophan hydroxylase isoform, TPH-2 mRNA, is increased by ovarian steroids in the raphe region of macaques. Molecular Brain Research. 2005;**135**:194-203. DOI: 10.1016/j.molbrainres.2004.12.011

[109] Bethea CL, Smith AW, Centeno ML, Reddy AP. Long-term ovariectomy decreases serotonin neuron number and gene expression in free ranging macaques. Neuroscience. 2011;**192**:675-688. DOI: 10.1016/j.neuroscience.2011.06.003

[110] Shively CA, Friedman DP, Gage HD, Bounds MC, Brown-Proctor C, Blair JB, Henderson JA, Smith MA, Buchheimer N. Behavioral depression and positron emission tomography-determined serotonin 1A receptor binding potential in cynomolgus monkeys. Archives of General Psychiatry. 2006;**63**:396-403. DOI: 10.1001/archpsyc.63.4.396

[111] Lima FB, Centeno ML, Costa ME, Reddy AP, Cameron JL, Bethea CL. Stress sensitive female macaques have decreased fifth Ewing variant (Fev) and serotonin-related gene expression that is not reversed by citalopram. Neuroscience. 2009;**164**:676-691. DOI: 10.1016/j.neuroscience.2009.08.010

[112] Gundlah C, Lu NZ, Mirkes SJ, Bethea CL. Estrogen receptor beta (ERβ) mRNA and protein in serotonin neurons of macaques. Molecular Brain Research. 2001;**91**:14-22. DOI: 10.1016/s0169-328x(01)00108-5

Chapter 4

Psychological and Social Aspects of Menopause

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69078

Abstract

Menopause is one of the age-related phases of physiological transition of females. There is robust research and information regarding its biological aspects specially its endocrine base, yet the psychosocial aspect is quite interesting and debatable due to its variability among different cultures and climates. There are certain subthreshold response in form fear and loss of reproductive life to no more ability to reproduce and a feeling of loss of femininity. The period of menstruation simulated to reproductive age or fertility is around half of their lives; therefore, loss of fertility or reproductive life may be a source of stress specially among tribes where long reproductive age period is desired on the cultural belief that this will lead to a large family size that is considered as a symbol of success. Psychological factors such personal or inter-psychic (personality, self-esteem, and coping skills) and intrapsychic (relationship issues and social support) may contribute in the onset, course, and repose to perimenopausal period. There are certain psychiatric conditions such as anxiety, depressive disorder, and premenstrual dysphoric syndrome related to premenopausal period that must be screened. Before embarking on pharmacological treatment, psychosocial intervention especially lifestyle modifications must be offered to avoid complications.

Keywords: menopause, psychosocial, women, depression, anxiety

1. Introduction

As female grows old with passing years, she undergoes different phases of life, from childhood to adulthood. Her body keeps on changing at all levels; may it be anatomical, physiological, and hormonal with the years of aging. Menopause is just another phase of life like puberty. It is the time when ovaries stop producing eggs any more.

Menopause is a Latin word where *"Meno"* means month and "*pause*" means to stop. Various terms have been used for menopause in different languages as "*Haiz ka band hona*" in Urdu, "*alssnn yas"* in Arabic.

It is neither a disease, an illness, a pathology, nor a state of being not well but just a normal physiological phenomenon of aging among females from transition of reproductive life to no more ability to reproduce. It has no impact on sexuality of a female. This transition occurs with some changes in hormones of female endocrine system predominantly estrogen leading to menopausal symptoms.

For women, the menopausal period is considered the climacterium, the middle adulthood; a period in life characterized by decreased biological and physiological functioning and may lead to psychosocial disturbance in form of interpersonal relationships [1]. It may start anywhere from the 40s to the early 50s but generally occurs between 47 and 53 years [1].

Considering the onset of menopausal age, one must keep in mind the difference between days per year in various calendars such as a lunar year of 354 days used by Muslims as compared to the solar year of 365 despite the fact that the later also known as Gregorian calendar is widely in use, but ancient calendars are also used by a significant number of peoples who belong to certain regions and religions, in the form of the Julian calendar, the Islamic calendar, etc.

The menopausal condition has been analog in men as andropause. For men, the climacterium has no clear demarcation; male hormones stay fairly constant through the 40s and 50s and then begin to decline [1].

All women will not experience menopause in the same way in terms of their onset and symptoms. Apart from a normal response or may be a positive feeling in the form of relief from pain or at least the burden of the management of menstruation each month, many premenopausal women have concerns that they will experience mental instability, sudden signs of aging, and diminution of sexuality at this time. Culture, health, previous experience of mood problems, lifestyle, and whether menopause onset is a natural, surgical, or chemotherapy-induced, will all impact on menopausal symptoms. Increased risk for psychiatric morbidity is seen in women who experienced early menopause or surgical menopause [2]. According to study of Bernice Neugarten, the famous American psychologist who is specialized in adult development and the psychology of aging, more than 50% of females described menopause as an unpleasant experience, some believed that their lives had not changed in any significant way, and many women experienced no adverse effects while some reports feeling sexually free after menopause of any worry of becoming pregnant.

2. Psychological factors

2.1. Personal psychological vulnerability

Large epidemiological studies have shown that the years usually associated with natural menopause, that is 45–55, are not associated with increased psychiatric morbidity or more utilization of health services by women [2–5]. Various personal factors of an individual female may affect her menopausal experience. Such as follows:

- Past experience of mood disorders.
- Negative attitude to menopause and aging: women with more negative attitudes toward the menopause in general report more symptoms during the menopausal transition [6].
- Life events, personality, and coping.
- Self-esteem: women with a low self-esteem used to have more severe menopausal complaints [7].

2.2. Life stressors

They may include the following:

- Lack of social support
- Unemployment
- Surgical menopause
- Poor overall health status

2.3. Interpersonal relationships

Social interpersonal relationships also have their impact on a person's life and general well-being. They constitute a major social support in a woman's life and help her in managing stressors and problems in life with influencial effect on psychological health. They may include the following:

- Relationship with a partner
- Relationship with children
- Relationship with friends/social support

Menopause could be a stressful transition due to various beliefs related to fertility and a gradual diminishing role or role shifts in society. Depression at menopause has been attributed to the *Empty Nest Syndrome.* A phenomenon observed with depression that occurs in some men and women when their youngest child is about to leave home. Many women, however, report an enhanced sense of well-being and enjoy opportunities to pursue goals postponed because of child rearing [1].

3. Social factors

Education and socioeconomic statuses are also important factors found to influence the intensity and symptoms of menopause [8]. The influence of psychological factors, lifestyle, body image, interpersonal relationships, role, and sociocultural factors in predicting levels of depression and anxiety in the menopause cannot be ignored.

Role, social factors, and culture have a great impact on menopausal symptoms, as few studies have shown rates of depressive symptoms and hot flashes or sweats were significantly lower among Japanese women than females of American and Canadian population [9]. Such variations across cultures may reflect differences in

- Beliefs and expectations regarding menopause and aging
- Status and roles of women in a particular society
- Sensitivity to specific symptoms
- Biology, diet, and health behaviors

In developing countries where there is low literacy rate, it has been observed that females expect conception even after menopause, and this may be because the success of woman was considered to be related to production of more children, particularly males.

The factors that must be considered while dealing with menopausal women are the following:

1. The variation in reproductive period, i.e., from onset of menses (also termed "menarche)" to menopause.
2. Variation in life expectancy among different countries, e.g., life expectancy of woman is as low as 50.8 years in Sierra Leone and as high as 86.8 years in Japan.

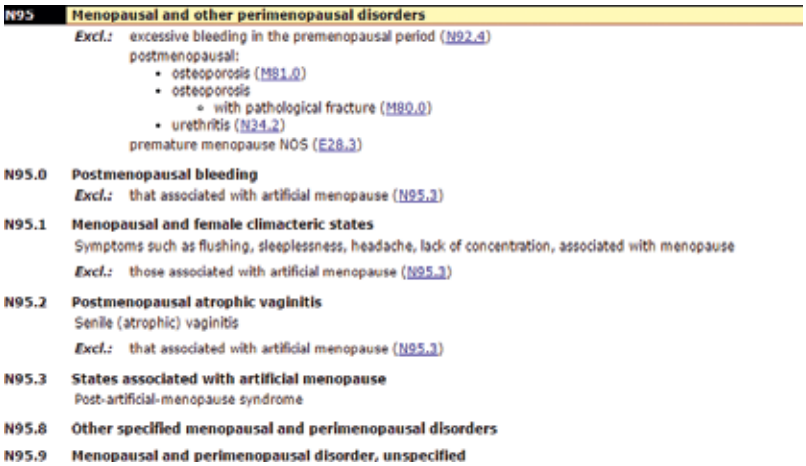
As reproductive life could vary significantly among the various countries, we may consider average menarche age as 13 years and age of menopause as 51 years, and on calculating the reproductive period of women in developing country with average life expectancy of 50 years, they would have reproductive life that is 74% of their total life in comparison to women of developed country with life expectancy of 86 years who would have reproductive life constituting only 44% of their life from birth.

With the above fact, the period of menstruation is simulated to reproductive age or fertility is around half of their lives; therefore, loss of fertility or reproductive life may be a source of stress specially among tribes, where long reproductive age period is desired on the cultural belief that this will lead to a large family size that is considered as a symbol of success.

4. Secondary effects on mood/psychiatric morbidity and menopause

Popular psychiatric nosology such as the WHO International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of Mental *Disorders* (DSM-5) is also ambiguous about this condition; therefore, insurance for its management need to be addressed. ICD-10 has a variety of coding for menopause and related menopausal disorders as shown in **Figure 1**.

Menopause is not a time of high risk for psychiatric illness but may be a time of psychological stress for women. Some women will experience psychological symptoms during the perimenopausal years [10]. Since mild emotional symptoms occur in many women during



N95 **Menopausal and other perimenopausal disorders**

Excl.: excessive bleeding in the premenopausal period (N92.4)
postmenopausal:
- osteoporosis (M81.0)
- osteoporosis
  - with pathological fracture (M80.0)
- urethritis (N34.2)

premature menopause NOS (E28.3)

N95.0 **Postmenopausal bleeding**
Excl.: that associated with artificial menopause (N95.3)

N95.1 **Menopausal and female climacteric states**
Symptoms such as flushing, sleeplessness, headache, lack of concentration, associated with menopause
Excl.: those associated with artificial menopause (N95.3)

N95.2 **Postmenopausal atrophic vaginitis**
Senile (atrophic) vaginitis
Excl.: that associated with artificial menopause (N95.3)

N95.3 **States associated with artificial menopause**
Post-artificial-menopause syndrome

N95.8 **Other specified menopausal and perimenopausal disorders**

N95.9 **Menopausal and perimenopausal disorder, unspecified**

Figure 1. ICD-10 coding for menopause and related disorders.

the perimenopausal years, it is important to establish whether the symptoms are of sufficient severity and duration to constitute major depression, generalized anxiety disorder, or panic disorder. Psychological distress is usually seen more in females with disturbed sleep [11]. Sleep could be disturbed in midlife due to psychosocial stressors of life or as a result of symptoms of menopause like hot flushes (also termed as "flashes") and night sweats. Female reproductive hormones and rapid changes in their levels may influence neurotransmitters in the brain, particularly the serotonin and gamma amino butyric acid systems. Estrogen modulates serotonin to increase serotonin presynaptic reuptake, modulates norepinephrine levels, decreases monoamine oxidase levels, affects dopamine turnover, increases brain excitability, affects endorphin levels, and possibly interacts with gamma amino butyric acid [12]. Progesterone is found to increase monoamine oxidase levels. In high doses, progesterone has an anesthetic effect and may decrease brain excitability through an interaction with the gamma amino butyric acid system [12]. The drop in estrogen levels during perimenopause and menopause can lead to hot flashes that disturb sleep. This can lead to anxiety, fears, and mood swings [1].

The greater frequency of symptoms during the years prior to the end of the menses and the reduction of symptoms once menopause has occurred suggest that emotional symptoms are related to changing hormone levels rather than low hormone levels [12].

Research has shown that reproductive hormones produced during menopause contribute to mood alterations, such as depression [13]. Menopausal status, however, remains an independent predictor of depressive symptoms [14]. Some women experience anxiety and depression, but women who have a history of poor adaptation to stress are more predisposed to the menopausal syndrome [1].

The two most common psychiatric conditions are anxiety and depression. Therefore, all the general physicians and gynecologists must ask two screening questions for each of these conditions from women of perimenopausal age, as suggested by experts, given in **Figures 2** and **3** (*in Urdu—for developing countries where Urdu language is medium of communication).

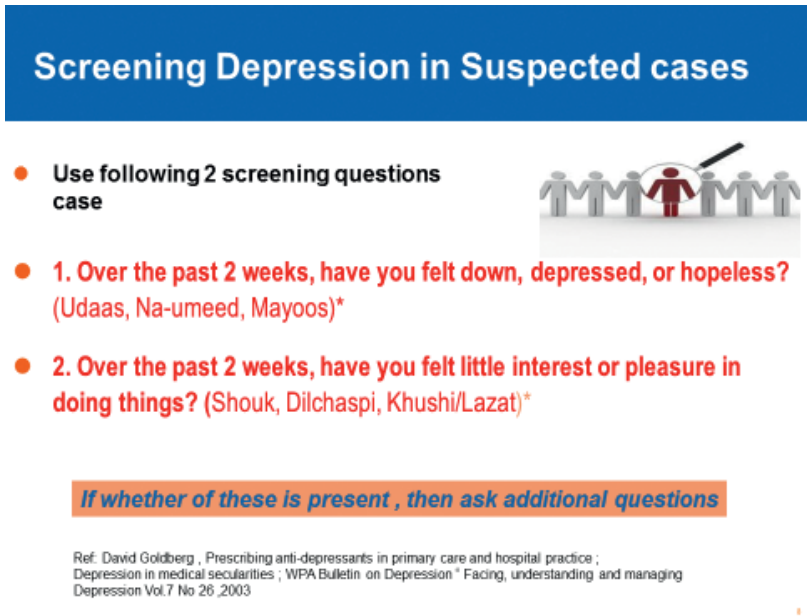


Figure 2. Screening questions for depression among perimenopausal cases (Urdu).

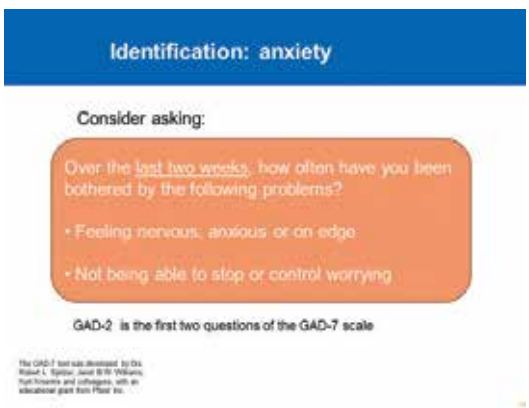


Figure 3. Screening questions for anxiety among perimenopausal cases.

4.1. Depression and the menopause

The changes that occur in hormone levels along with general health, shifts, and stresses of family life in a woman's menopausal years as a whole effect the onset of depression among them [15]. According to a study at Harvard on Moods and Cycles constituting premenopausal women aged 36–44 years with no history of major depression with a follow-up of these women for 9 years to detect new onsets of major depression. Clinically significant depressive symptoms likely to develop among perimenopausal women were twice as common than women who had not yet gone under menopausal transition [16].

Typical symptoms of depression include depressed mood, anhedonia, and fatigue. Reaching diagnosis of Depressive Disorder, two internationally recognized criteria are of ICD-10 and DSM-5. Symptoms should be there for at least 2 weeks and leading to poor social or occupational functioning and condition should not be due to any substance use. Presence of at least two typical expressions with two common symptoms constitutes the criteria of Major Depressive Disorder (F32) according to International Classification of Diseases version 10 (ICD-10), while presence of at least one typical and five or more common symptoms constitute criteria to diagnose Depressive Disorder in Diagnostic and Statistical Manual (DSM). List of Symptoms is shown in **Figure 4**.

4.2. Anxiety and the menopause

Women who are more anxious experience greater extent of menopausal symptoms. Many of the symptoms of anxiety and menopause coincide like sweating, palpitations (increased heart rate), restlessness, sleep disturbance, which may confuse some. But no correlations have been found in between hormonal changes during menopause with incidence of anxiety disorder. Other psychosocial factors may contribute in development of anxiety among females of midlife.

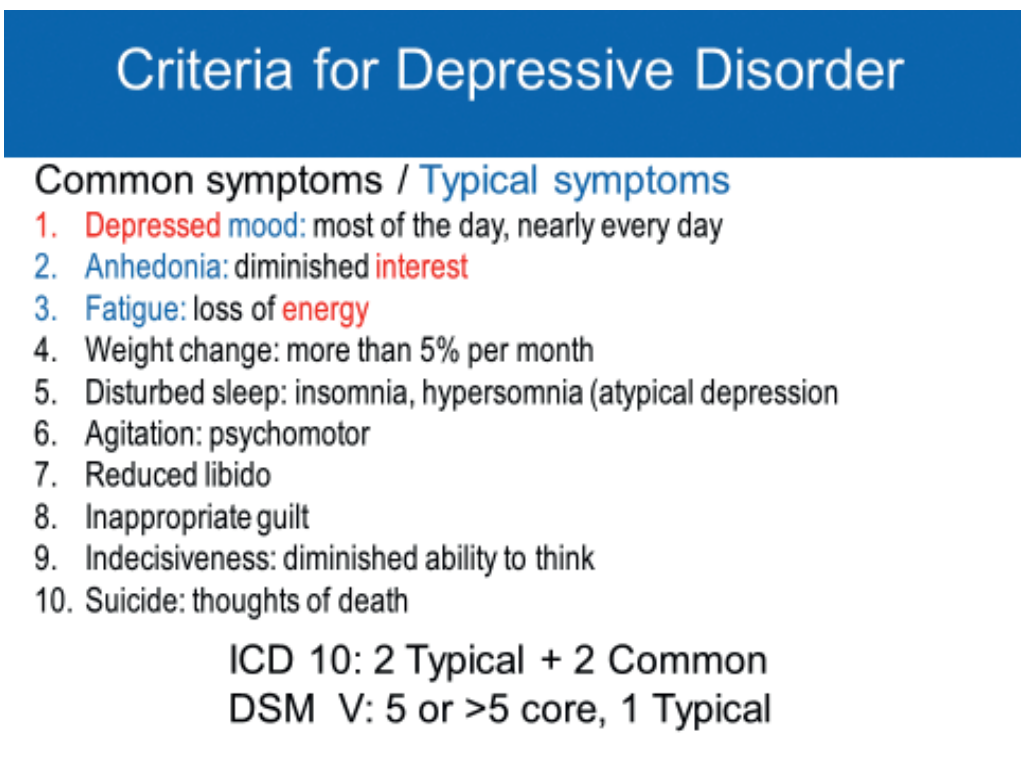


Figure 4. ICD-10 and DSM diagnostic criteria for depressive disorder.

Symptoms of anxiety include the following:

- apprehension
- irritability
- impatience
- fearfulness
- restlessness
- difficulty concentrating
- trouble falling asleep
- increased frequency of urination
- hyperventilation
- sweating, especially in the palms
- muscle tension

The symptoms of anxiety and depression may sometimes coincide and may be present simultaneously so if asked what are the defining symptoms of anxiety and depression? The clear difference and presentation of symptoms have been described in **Figure 5** with various differences and the similarities of anxiety and depressive disorder.

Anxiety & Anxiety Disorder	Depression
Feeling of fear, apprehension and excessive anxiety energy	Feeling of emptiness, deep sadness or misery, loss of hope
Physical feelings of agitation, muscle tension and symptoms of anxiety eg. heart symptoms, nausea, dissociation, diarrhoea, breathing difficulties etc	Slowing down of physical movement and lack of physical energy
General sense of being tense and rigid	Physical body slumped
May be a perfectionist and is concerned about the results of activities (can lead to poor performance)	Loss of interest and ambition (can lead to poor performance)
May fear death but not focused on suicide (Suicide thoughts come only when Depression is a secondary effect of anxiety disorder)	Suicidal thoughts present in deep depression

Figure 5. Features that differentiate anxiety and depression.

4.3. Other psychiatric conditions

Apart from anxiety and depressive disorder, the other psychiatric conditions that have been linked to menopause are premenstrual dysphoric syndrome and surprisingly a rare condition Trichotillomania discussed as under.

Premenstrual dysphoric syndrome: it is a condition of changing mood with changes in hormone levels every month before menstruations.

Anecdotally, many cases as they approach to menopause report that their symptoms of premenstrual dysphoric syndrome worsen at onset of perimenopause and alleviate with menopause [17].

Trichotillomania (hair-pulling disorder) symptoms may worsen at perimenopause [17].

5. Biopsychosocial aspects in management of symptoms of menopause

The art of assessing menopausal symptoms and menses may be threatening in some culture; therefore, reaching this condition needs proper working and skills which are less cumbersome because in general females are sensitive about aging process and loss of fertility.

5.1. Pharmacological interventions

5.1.1. Hormone replacement therapy

Estrogen and androgen alone or in combination of both is found to be more effective in improving symptoms in nonclinically depressed perimenopausal and menopausal women according to meta-analysis [18] of various studies on effects of hormone replacement therapies on mood. Progesterone had a much smaller effect, and when combined with estrogen, reduced the positive effects of the estrogen. The most robust effect was noted with androgen, either alone or in combination with estrogen.

Studies have shown that combined estrogen-progestin drugs (e.g., premarin) cause small increases in breast cancer, heart attack, stroke, and blood clots among menopausal women. Studies of the effects of estrogen alone in women who have had hysterectomies (because estrogen alone increases the risk for uterine cancer) are ongoing [1].

5.1.2. Antidepressants

Depression during perimenopause and menopause is treated in much the same way as depression that strikes at any other time.

Although symptoms of depression are relieved by a majority of antidepressants including SSRIs such as Fluoxetine, Paroxetine, SNRIs, e.g., venlafaxine, des-venlafaxine, and TCA as amitriptyline, but desvenlafaxine (the dual serotonin and norepinephrine reuptake inhibitor)

is used popularly, off label, for symptoms of depression with menopause despite the fact that the US Food and Drug Administration (FDA) has denied an application for its use for the treatment of moderate-to-severe vasomotor symptoms such as hot flashes associated with menopause.

A meta-analysis shows that desvenlafaxine was associated with a statistically significant reduction in the number and severity of daily moderate-to-severe hot flashes. The number of nighttime awakenings because of hot flashes was also significantly decreased. However, the rate of desvenlafaxine treatment discontinuation because of adverse events was significantly higher than placebo-treated women and the risk ratios of adverse events such as asthenia, hypertension, anorexia, constipation, diarrhea, dry mouth, nausea, dizziness, insomnia, somnolence, and *mydriasis* (the dilation of the pupil) were very high [19].

5.2. Nonpharmacological interventions

5.2.1. Lifestyle modifications

A healthy lifestyle can help to reduce symptoms of menopause

1. Exercise

- Being physically active helps with hot flushes, stress, and mood
- Exercise has beneficial effects on hot flashes, well-being, Body Mass Index (BMI) and Coronary Heart Diseases risks [20]
- Activities that stimulate the brain can help rejuvenate memory such as doing crossword puzzles, longhand mathematics, and reading books.

2. Diet

- A nutritious diet helps with fatigue and moodiness.
- A healthy diet, low in fat, high in fiber, with plenty of fruits, vegetables, and whole-grain foods.
- Intake of foods with phytoestrogen.

  Phytoestrogens are estrogen-like substances found in some cereals, vegetables, legumes (including soy), and herbs. They might work in the body like a weak form of estrogen. The first widely attributed health benefit of phytoestrogen consumption was relief from vasomotor perimenopausal symptoms, including hot flushes and night sweats. Moderation is a likely key and the incorporation of real foods, as opposed to supplements or processed foods to which soy protein is added, is probably essential for maximizing health benefits [21]. Consumption of 30 mg/day of soy isoflavones reduces hot flashes by up to 50% [22].

- Ensure enough calcium and vitamin D intake on regular basis

- Avoid smoking and alcohol, as it is known to make hot flushes worse
- Foods that should be avoided in menopause
  - Caffeine
  - Spicy foods

5.2.2. Social support

- Social interactions with family and community, nurturing relationship, and healthy emotional support from friends are very effective means. A professional help from a counselor and mental health professional is quite effective and must be readily available. Misconception as described by individuals as potentially difficult, embarrassing, and stigmatized leading to fear and avoidance in some individuals at developing countries must be addressed.

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References

[1] Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Synopsis of Psychiatry; Behavioral Sciences/Clinical Psychiatry, 11th ed. Philadelphia: Wolters Kluwer; 2015

[2] McKinlay JB, McKinlay SM, Brambilla D, et al. The relative contributions of endocrine changes and social circumstances to depression in mid-aged women. Journal of Health and Social Behavior. 1987;**28**:345-363

[3] Hallstrom T, Samuelson S. Mental health in the climacteric: The longitudinal study of women in Gothenburg. Acta Obstetricia et Gynecologica Scandinavica. 1985;**13**:130-135

[4] Kaufert PA. A health and social profile of the menopausal woman. Experimental Gerontology. 1994;**29**:343-350

[5] Nicol-Smith L. Causality, menopause, and depression: A critical review of the literature. BMJ. 1996;**313**:1229-1232

[6] Ayers B, Forshaw M, Hunter MS. The impact of attitudes towards the menopause on women's symptom experience: A systematic review. Maturitas. 2010 Jan;**65**(1):28-36

[7] RosemeierHP, Schultz-ZehdenB. Psychological aspects of menopause. In: FischlFH, ed. Menopause-Andropause: Hormone Replacement Therapy Through The Ages. Gablitz: Krause & Pachernegg GmbH. 2001

[8] Dennerstein L. Wellbeing, symptoms and the menopausal transition. Maturitas. 1996;**23**: 147-157.

[9] Avis N, Kaufert PA, Lock M, McKinlay SM, Vass K. The evolution of menopausal symptoms. Baillieres Clinical Endocrinology and Metabolism. 1993;**7**:17-32

[10] Diana C. Depression and emotional aspects of the menopause. BCMJ. 2001 Oct:**43**(8); 463-466

[11] Bromberger JT, Meyer PM, Kravitz HM, et al. Psychologic distress and natural menopause: A multiethnic community study. American Journal of Public Health. 2001 Sep; **91**(9):1435-1442

[12] Pearlstein TB. Hormones and depression: What are the facts about premenstrual syndrome, menopause, and hormone replacement therapy? American Journal of Obstetrics and Gynecology. 1995;**173**:646-653

[13] Gordon JL, Girdler SS, Meltzer-Brody SE, Stika CS, Thuston RC, Clark CT, et al. Ovarianhormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: A novel heuristic model. American Journal of Psychiatry. 2015 Mar; **172**(3):227-236.

[14] Bromberger JT, Schott LL, Kravitz HM, Sowers M, Avis NE, Gold EB, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: Results from the Study of Women's Health Across the Nation (SWAN). Archives of General Psychiatry. 2010 Jun;**67**(6):598-607

[15] Kaufert PA, Gilbert P, Tate R. The Manitoba project: A reexamination of the link between menopause and depression. Maturitas. 1992;**14**:143-155

[16] Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: The Harvard study of moods and cycles. Archives of General Psychiatry. 2006;**63**:385-390

[17] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing. 2013

[18] Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology. 1997;**22**:189-212

[19] Berhan Y, Berhan A. Is desvenlafaxine effective and safe in the treatment of menopausal vasomotor symptoms? A meta-analysis and meta-regression of randomized double-blind controlled studies. Ethiopian Journal of Health Sciences. 2014 Jul;**24**(3):209-218

[20] Dennerstein L, Lehert P, Guthrie JR, et al. Modeling women's health during the menopausal transition: A longitudinal analysis. Menopause: Journal of the North American Menopause Society. 2007;**14**(1):53-62

[21] Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. Frontiers in Neuroendocrinology. 2010 Oct;**31**(4):400-419

[22] Kurzer MS. Soy consumption for reduction of menopausal symptoms. Inflammopharmacology. 2008 Oct;**16**(5):227-229

Chapter 5

Depression and Serotonergic Changes during the Climacteric and Postmenopausal Stages: Hormonal Influences

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69786

Abstract

Depression is a psychiatric disorder that affects a high percentage of women. Most of the depression disorders turn up during the premenopause and perimenopause stages when the hormonal oscillations make an impact in the brain function principally on the serotonergic system, which is related to neurobiology of depression. 5-HT1A and 5-HT2A receptors change on functionality and density in afferent areas related to emotional modulation and increased serotonin clearance, and the binding potential of serotonin transport has been related to the underlying mechanism of the depression during the climacteric or postmenopausal stage. Some findings have been proven on preclinical studies. These studies on animals have recognized how estrogen treatment activates intracellular signaling pathways as mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK), tyrosine kinase brain-derived neurotrophic factor receptor (TrKB), insulin-like growth factor-1 receptor (IGF-1R), phosphatidylinositol 3-kinase (PI3)/serine/threonine-specific protein kinase (Akt), and metabotropic glutamate receptor 1 (mGluR1) which interact with the serotonergic system to allow establishment of the estradiol effects on mood regulation. Thus, the interaction between the woman's reproductive status and the serotonin changes could be useful to create prevention strategies, early diagnosis, and medical treatment of climacteric and postmenopausal women with depression, in order to improve their quality of life.

Keywords: depression, menopause, climacteric, 5-HT1A receptor, 5-HT2A receptor, estradiol

1. Introduction

Depression is one of the most common psychiatric disorders that affect approximately 4.84% people around the world, and it is considered to be one of the principal causes of disability worldwide [1]. According to the Global Burden of Disease study report in 2015 [2], the highest rates of disability-adjusted life years (DALYs) worldwide are established on women aged 15–49 years with 5.65%, followed by 50–69 years old women with 2.98% and 70 years old with 1.26%. DALYs represent the years of life that are adjusted by a certain level of disability experienced during a particular period of time, related to depressive disease. It supports studies which demonstrate that most of the depression disorder comes out during the premenopause and perimenopause stages.

During the beginning of menopausal stage or in the postmenopausal stage, women are more susceptible to suffer depression disorder with more severe and longer symptoms [3, 4]; severity of depression has been related to the ovarian hormone oscillating levels in the premenopause and very low levels in early postmenopause, specifically with estrogens [5].

The climacterium stage is a period of time that includes the perimenopause, premenopause, and menopause (see **Figure 1**); in this stage the women estrogenic oscillating, produces a dysfunction on the serotonergic neurotransmission system which is related to the high prevalence of depression in such stages compared with women in postmenopausal stage. However, this relationship seems to be controversial because not all the studies reported an increased prevalence of depression in the climacteric stage, when women's groups from different ethnic cultures, ages, school grade, and civil status, among others, were evaluated. These divergences on the clinical study results could be partially justified by different neurochemical changes related to the effects of estradiol on serotonergic system and the influence of these changes on the establishment of depression during the different stages of the climacteric period. For example, on early premenopausal stage, there is a decrease on the 5-HT1A autoreceptors in raphe, which is a brain structure responsible for the serotonin (5-HT) synthesis, and an increase on the 5-HT1A postsynaptic receptors located on the hippocampus (both receptors enable the antidepressant clinically effective, as the selective inhibitors of the serotonin, e.g., the fluoxetine) related to the high hormonal concentration compared with postmenopausal women [6].

				Climacterium						
				Premenopause	Perimenopause					
STAGE	**REPRODUCTIVE**				**TRANSITION TO THE MENOPAUSE**			**POSTMENOPAUSE**		
Phase	Early	Peak	Late		Early	Late	**Menopause**	Early		Late
Duration	Variable	Variable	Variable	Variable	Variable	1 - 3 years	1 year	1 year	3-6 year	Till the end of life

Figure 1. Classification of the reproductive phases of the woman. This classification is an abstract of the reproductive stage of women with their approximate during. Ovaries function markers and hormonal levels can help to make a correct classification. Modified from [57].

http://dx.doi.org/10.5772/intechopen.69786

Thus, this can be related with the different antidepressant responses along the climacteric and postmenopausal stages.

The 5-HT2A receptors located on brain areas such as prefrontal cortex contribute on regulating the release of the 5-HT to areas that modulate the amygdala reactivity, brain structure involved to the emotional regulation. Treatment with 17β-estradiol for postmenopausal women increases the 5-HT2A receptors in prefrontal cortex [7]. However, the possible association between the establishment of depression in different climacteric and postmenopausal stages with the 5-HT2A receptor's activity has not been explored. Nevertheless, the preclinical data support the involvement of these receptors on the regulation of the depression disorder [8, 9].

On the other hand, in healthy postmenopausal women, there is a relation between personality features such as extroversion, aggressiveness, and neuroticism with the serotonin transporter (5-HTT). 5-HTT promotes polymorphism with "s" allele, which implies 5-HTT low expression and an increase in the impulsivity. Likewise, this trait is related with monoamine oxidase A (MAO-A) polymorphism that produces an increase of climacteric and depressive symptoms [10, 11]. In contrast, women under 50 years old with the "l" allele 5-HTT present a better antidepressant response and neural protection against the suicide attempt [12]; however, this response disappears when there is a low hormonal activity during menopausal stage [13].

Therefore, the main objective of this work is to collect and review scientific data not only clinical but also preclinical data that allow us to explain the knowledge about the impact of hormonal change experienced during climacteric and postmenopausal stages and how it affects serotonin neurotransmission that may contribute to the establishment of the depression disorder and the therapeutic response to antidepressant drugs.

2. Influence of hormones on the depression disorder establishment

Some researches point out a high vulnerability to suffer depression disorder on the women reproductive stage, related to the hormonal changes, as a decrease on the estradiol levels and an increase on the follicle-stimulating hormone (FSH) levels on the perimenopausal [3, 14, 15] throughout different reproductive stages it is set basically two different aspects about the hormonal influences, principally estradiol with the increasing risk to set out depressive symptomatology. The first one establishes that low hormonal concentrations on estradiol and progesterone during the earlier follicular stage of the menstrual cycle of the earlier productive stage of a woman are related to premenstrual dysphoric syndrome characterized among some other symptoms by depression and anxiety [16]. The second one suggests that oscillations on the hormonal levels on early stages of the menopause transition are determinant to increase the risk of having some depressive incidences. The same effect is observed on women who had been throughout menopause by surgical procedure, thus, became on the decrease of the hormonal levels, and also there is a surgical post-period where they show hormonal oscillations because the renal glands try to supply the hormonal

lost, but it is important to mention that women who had been in a surgical procedure, such as oophorectomy on early age, indicate an increased probability to depression disease with severe and longer symptoms compared to women with a natural menopause [17].

There is a relationship at the establishment on depressive symptomatology with FSH or high luteinizing hormone (LH) levels and low inhibin B levels; this is a glycoprotein hormone secreted by teak and granulosa cells from the pre-antral and antral follicles that was responsible for the inhibition of FSH production at the level of the pituitary gland and a huge variability on estradiol levels, which occur during the menopause transition that includes women on the premenopause and perimenopause [2, 3]. Likewise, there is a FSH levels increasing and an abrupt fall of the estrogen levels after 12 months of menopause considered as early postmenopausal [18] pattern, which is independently from the sample analyzed on the late premenopausal and postmenopausal stage. Those hormonal variations are related to a rise on depression prevalence for 10 years before and 8 years after the last menstrual cycle and fall on the late postmenopausal period [4]. The above suggests that alterations in the feedback of the hypothalamic-pituitary-gonadal axis consequence of changes on the concentrations of ovarian hormone through the climacteric and postmenopausal stages, carry out a fundamental place on women's emotional stability, through the regulation of brain plasticity and neurochemical changes.

It has been established an association between a delay in appearance of menopause transition, in a period of two more years than average with 2% of decrease on the risk of a depression disease during the postmenopause, and also a reduction of the 50% to suffer depression disease on women who have menopause after 40 years old compared with early menopause on women before that age. It is suggested that those findings could be attributed to longer exposure to the endogenous estrogens that develop a neural protection and antidepressive effect [19]. This effect seems to be associated with the cerebral changes that induce the hormonal diminution according to the age of the woman.

The antidepressant effect on hormone replacement therapy (HRT) or estrogenic therapy on menopausal women is controversial. The estrogen supply such as 17β-estradiol (100 μg/day) has a lack of antidepressant effects on depressed women during the postmenopausal period on the late stage; it is to say that, 17 years after the menopausal stage, they show a FSH (≥40 pg/ml) and estradiol (≤19.7 pg/ml) hormonal concentrations [20]. This lack of antidepressant effect is also observed in postmenopausal women in the early phase, approximately 6 months to 3 years after menopause, with hormonal concentrations of FSH ≥ 35 pg/ml and estradiol ≤ 40 pg/ml, when 50 μg/day or 84 μg/day of estradiol was administered [7, 21]. The loss of estrogen efficacy against depression in women with postmenopausal may be associated with the downregulation of α- and β-estrogenic receptors at the brain level, caused by continued decrease of plasma estradiol concentrations. In contrast, antidepressant effects have also been reported in postmenopausal women with replacement treatments with bioidentical hormones (80% estriol/20% estradiol; 0.25 to 0.5 mg) and/or progesterone (20 to 60 mg), by transdermal injection in a volume of 1 ml/day for a period of 8 weeks. These women present an improvement in the depressive and anxiety symptoms according to Hamilton scales, at 2 months of treatment and annually until 36 months. Treatment with bioidentical hormones improved the health and quality of life of

women without reports of adverse side effects. However, these women cursed postmenopausal, after an oophorectomy with a mean age of 52.3 ± 9.6 years and the time that elapsed since the surgery was not described, so it cannot be specified whether it was in the early or late stage of postmenopause [22]. This suggests that the type of molecule used for hormone replacement therapy and probably the age at which it is given could determine therapeutic success, a possibility that remains to be explored.

Changes in plasma levels of FSH on the establishment of depression in women with natural menopause are also seen in women with oophorectomy [23]; since the ovaries are removed, there is an abrupt cessation in the production of testosterone that is aromatized to estrogen and estradiol, which results in a dysfunction in the hypothalamic-pituitary-gonadal axis increasing FSH and LH levels, with the consequent decline of estradiol and progesterone levels [24]. These changes in hormone levels undergoing surgery take from 2 to 3 months to stabilize and are associated with a decrease in depressive symptoms [23]. Women undergoing menopause induced by surgeries such as hysterectomy and/or oophorectomy increase up to four times the probability to suffer postsurgery depression [25]. However, women who have undergone some depressive episode prior to surgery report a decrease in postoperative depressive symptomatology [25]. This may reflect a paradoxical effect. Some of the answers might be in the interrelation between estrogen and the serotonergic system.

3. Serotonergic alterations during the climacteric and postmenopause related with depression

A study by Stein et al. [6] detected an increase on 5-HT1A receptor levels in the hippocampus and a decrease in the dorsal nucleus raphe of premenopausal women at early ages (24.1 ± 2.6 years) compared to postmenopausal women (55.2 ± 4.8 years). In this same study, they identified higher concentrations of progesterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and cortisol in premenopausal women compared to postmenopausal women. This suggests that these hormones could be involved in the regulation of the expression of 5-HT1A receptors in different brain areas in women who travel through the climacteric, intervening in the establishment of depressive disorders of this stage, as well as in the different therapeutic responses to antidepressant drugs, and probably contributing to the effect of drug resistance, depending on the levels of receptors affected by oscillations on concentrations of hormones, mainly produced by the ovaries.

Studies made with positron emission tomography with [carbonyl-C11] WAY-100635 show that in the dorsal nucleus raphe, a structure highly involved in the regulation of serotonergic neurotransmission and therefore with a high density of 5-HT1A receptors, there is 1.5 times more 5-HT1A receptors in the luteal phase than in the follicular phase in healthy women, whereas this proportion is not observed in women with premenstrual dysphoric disorder [26], so a dysfunction like this could be a factor underlying to the establishment of depressive symptoms. Although Drevets et al. [27] reported a reduction in 5-HT1A receptors in the raphe (41.5%) and neocortical and limbic areas (25–33%) in depressed patients [27]. In this study the

sex of the patients was not discriminated, and only from 4 to 7% of the patients were women and do not described the age neither conditions of the reproductive phase, so these results should be taken with reservation.

Moses-Kolko et al. [28] reported that in depressed women going through premenopause and postmenopause, there is a 15% decrease in 5-HT1A receptors in the orbitofrontal cortex compared to adult men with depression. The foregoing after performing an endocrine standardization to minimize the influence introduced by endogenous hormonal fluctuations and reproductive stage. They also detected an increase in the potential binding to 5-HT1A receptors in women, as age increases. They estimate that there is a 4.5% reduction per decade of age in the number of 5-HT1A receptors in the raphe in women. The 5-HT1A receptors have an age-dependent increase in neocortical regions in women, associated with decreased estrogen. In the same study, they identified that increase in 5-HT2A receptors is associated with the establishment of disorders such as neurosis, depression, suicide, and eating disorders [28], suggesting that age tends to reduce these receptors, since they are expressed in the neuropil of pyramidal neurons located mainly in the neocortex which are related to the release of glutamate and gamma-aminobutyric acid (GABA) regulating the postsynaptic excitatory impulses that project to the hippocampus and spinal cord neurons [29]. So, it is hypothesized that its reduction associated with age may be related to sleep disorder, cognition, and mood disorders [30].

4. Serotonergic changes associated to antidepressants and hormone replacement in the climacteric and postmenopause

The HRT in women undergoing climacteric, with 17β-estradiol by means of transdermal patches at a mean dose of 93 μg/day, causes an increase in plasma levels of estradiol from 14.7 pg/ml at baseline versus 176.5 pg/ml, after 10.2 weeks of treatment. This increase in estrogen levels has been related to the establishment of antidepressant effects after HRT [7]. However, several studies suggest that estrogens have the capability to produce a modulating effect on the serotonergic system that contributes to the establishment of the antidepressant effect (see **Table 1**).

In surgically postmenopausal women (58.4 age and 7.5 years after oophorectomy) and, therefore, with very low plasmatic concentrations of estradiol, the treatment with estradiol reduces the potential binding of 5-HTT in brain structures, such as in the amygdala, in the frontal cortex, and in various cortical regions. While the treatment with estradiol and testosterone reduces it in the parahippocampal gyrus, insular cortex, caudate nucleus, and thalamus [31]. Hence, the hormonal treatment reduces the efficiency of 5-HTT and increases the availability of 5-HT in the synaptic cleft on structures involved in the emotion modulation. This fact could be associated to an improvement in depressive symptomatology of these women measured with Beck Depression Inventory test [31]. However, some studies indicate that estrogen therapy in postmenopausal women does not produce antidepressant effects [21, 24], probably due to the downregulation of estrogenic receptors, associated with chronic decrease of

Changes associated to condition without pharmacological treatment

Condition (average age)	Serotonergic system	Hormonal changes	References
Premenopausal women (24.1 ± 2.6 years) vs. postmenopausal women (55.2 ± 4.8 years)	↑ 5HT1A receptor levels in the hippocampus ↓ 5HT1A receptor levels in the dorsal raphe	↑ Levels of progesterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and cortisol	[6]
Premenopausal depressed women (<50 years) Postmenopausal depressed women (>50 years)	↓ Postsynaptic 5-HT1A receptors in neocortical regions Increasing age was associated with↑ postsynaptic 5-HT1A receptor binding potential in neocortical regions Significant decline in 5HT2A receptor binding potential relative to age (8% per decade)	Low estradiol concentrations and low 5HT1A receptor binding potential	[28]

Changes associated to condition and estrogen replacement therapy

Condition (average age)	Serotonergic system changes	Regimen of treatment and/or changes associated to treatment	References
Surgically postmenopausal women (58.4 ± 4.7 years) Hysterectomy and bilateral oophorectomy	↓ The binding potential of 5-HTT in the amygdala, parahippocampal gyrus, insular cortex, and frontal cortex and in various cortical regions	Positive correlation between estradiol levels and the binding potential of 5-HTT in putamen, frontal cortex, and amygdala Negative correlation between testosterone levels and the binding potential of 5-HTT in the anterior cingulate cortex, hippocampus, caudate nucleus and thalamus	[31]
Postmenopausal women (54.5 years, 44–68 age range)	↑ 5-HT2A serotonergic receptors mainly in brain areas such as the right inferior prefrontal cortex, anterior cingulate cortex, and medial and inferior frontal gyrus	Transdermal patch (17β-estradiol, 0.075–0.15 mg; mean dose=0.084 mg for a mean of 10.2 weeks Negative correlation between estradiol levels and 5HT2A receptors	[7]
Postmenopausal women (55 ± 4.8)	No significant differences in 5-HT1A binding potential values	Combination 17β-estradiol valerate (Progynova® 21 mite; 2 mg/day, v.o.) and micronized progesterone (Utrogestan®, 200 mg/day, v.o.) for 67 ± 8 days Increase in estradiol and progesterone plasma levels	[56]
Female rats (2–3 months) Five postovariectomy days	↓ The time of 5-HT1A receptor desensitization of 7 days with fluoxetine and 2 days with estradiol + fluoxetine	17β-Estradiol-3-benzoate (0.01 mg/0.4 ml/kg, s.c.) plus fluoxetine (10 mg/2 l/kg, s.c.)	[37]
Female rats (2 months) Two months of postovariectomy	↑ 5-HT level in raphe	Estradiol benzoate (2.5 μg/kg/0.1 ml, s.c., day of ovariectomy; 5 μg/kg/0.1 ml, s.c., weekly; 20 μg/kg/0.1 ml, s.c. day of the test) + Progesterone (2 mg/kg/0.1 ml, s.c., 48 hours before the test)	[40]

Changes associated to condition and estrogen replacement therapy

Condition (average age)	Serotonergic system changes	Regimen of treatment and/or changes associated to treatment	References
Female rats (1–2 months) 2–3 weeks of postovariectomy	Slowing of the 5-HT clearances, as well as an inhibition of the ability of fluvoxamine (SSRI antidepressant) to slow the clearance of 5-HT	Acute administration of both 17β-estradiol in the CA3 region of the hippocampus and systemic administration of estradiol benzoate (25 μg/100 μl, s.c., 48 hours before progesterone) + progesterone (500 μg/100 μl, s.c., 24 hours before the test)	[41]
Female rats (2–3 months) 2–3 weeks postovariectomy	Canceled the antidepressive-like effect of fluvoxamine (10 mg/kg) in forced swim test	Estradiol benzoate (25 μg/100 μl, s.c., 74–75 hours before the test and 24 hours before progesterone) + progesterone (500 μg/100 μl, s.c., 24 or 74–75 hours before the test)	[42]
Female rats (4 months) Two weeks of postovariectomy	Inhibits the 5-HTT	Estradiol (20 pmol) in the CA3 region of the hippocampus but not in 10 months in females, even at <40 pmol doses	[51]

5-HTT, serotonin transporter; 5-HT, 5-hidroxytriptamine; ↑, increase; ↓, decrease; SSRI, selective serotonin reuptake inhibitors

Table 1. Clinical and preclinical studies of the relation between serotonergic system and hormones.

concentrations of estradiol in the postmenopausal stage. This hypothesis is based on the fact that estrogenic antidepressant treatment on perimenopausal women produces therapeutic effects [32], probably because they still have considerable concentrations of estradiol, compared to postmenopausal women, which contribute that they do not present important neurochemical changes on estrogen receptors. In support, depressed postmenopausal women treated simultaneously with the combination of antidepressant serotonin-specific reuptake inhibitor drugs, such as fluoxetine with estrogen, showed significantly greater improvement of both mood and quality of life compared to fluoxetine monotherapy [33]. Pointing out that estrogen by itself probably does not produce antidepressant effects, the reduction that exerts on the potential binding of 5-HTT is enough to increase synaptic 5-HT concentration, a synergistic effect on serotonergic system of both estrogen and fluoxetine, which contributes to the establishment of the antidepressant effect. Paradoxically, the combination with tibolone, a synthetic steroid, does not produce synergistic antidepressant effects with fluoxetine [34]. The above suggests that substituents on steroid molecules could be a determinant in the potential interrelation in therapeutic efficacy between steroids and the serotonergic system.

On the other hand, some studies observed an increase on hypersensibility of postsynaptic 5-HT2A receptors on the basis of neurobiological depression [35, 36]. The 5-HT2A receptor is related to regulating the 5-HT release on the protection of neurons which are located on the prefrontal cortex, thus, to help the regulation easier to the amygdala's reaction and some other behaviors related. The administration of 150 mg/day of clomipramine for 3 weeks, tricyclic antidepressant, results a descend of 5-HT2A receptor's occupation on neocortex area,

calculated by positron emission tomography (PET) which coincide with depression scores significantly improved, denoting the probability of the clomipramine's interaction with those receptors or may cause modified signal mechanism of these receptors [37].

There is a relationship with ovarian hormone and the 5-HT2A receptors. Kugaya et al. [7] developed a study on postmenopausal women, classified by the concentrations of FSH ≥30 UI/L. Those women were treated with 17β-estradiol HRT for almost 3 months; by PET that 5-HT2A serotonin receptors increased principally on brain areas such as prefrontal cortex and anterior cingulate cortex, related to increase of plasmatic estradiol density, this study did not mark any changes related to the effects on the mood but could be the result related to the test characteristics and the few subjects of study [7].

5. Preclinical studies of serotonergic changes associated with hormones and ovariectomy

Studies made in rodents have also shown the interrelation between estrogen and serotonergic system. Coadministration of estradiol with fluoxetine has been shown to contribute to 5-HT1A receptor desensitization [38], which is associated with antidepressant effect in humans and in rats evaluated in behavioral despair models [38]. In addition, this combination of estradiol with fluoxetine inhibits 5-HTT and increases de novo brain serotonin synthesis by activating tryptophan hydroxylase enzyme [39]. At the same time, it increases the number and sensitivity of the 5-HT1A receptors, mainly in the dorsal nucleus raphe of rats. This could be related to the antidepressant effect produced by estradiol.

It has also been detected that acute administration of estradiol on ovariectomized rats increased the turnover of serotonin, by increasing serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in amygdale and striatum involved in the mood regulation. While chronic for 16 days, estradiol and progesterone administration has been found to increase serotonin mainly in the dorsal raphe of the ovariectomized rats [40].

Benmansour and collaborators' research group [41] has explored the signaling mechanisms involved in the interaction of estradiol and serotonergic systems in rats. Both acute administration of 17β-estradiol in the CA3 region of the hippocampus and systemic administration of estradiol benzoate cause slowing of the 5-HT clearances, as well as an inhibition of the ability of fluvoxamine to slow the clearance of 5-HT [41]. These effects are mediated by estrogen receptors α and β. The slowing of the 5-HT clearance was due to activation of β-estrogen and/or GPR30. Meanwhile, the blockade of fluvoxamine's inhibitory effect on 5-HT clearance was mediated by α-estrogen [42]. Both of them used different signaling mechanisms. The estradiol-induced slowing of serotonin clearance by means of activation of receptors of β-estrogen required MAPK/ERK1/2 signaling pathways and involved interactions both with tyrosine kinase BDNF receptor (TrKB) and insulin-like growth factor-1 receptor (IGF-1R). The effect of estradiol to prevention of the ability of fluvoxamine to slow serotonin clearance, through receptors of α-estrogen, required MAPK/ERK1/2 and PI3K/Akt signaling pathways as well as interactions with both IGF-1R and mGluR1 [43]. All these ways are etiologically implied to depression.

In this context, the ERK signaling cascade is activated by antidepressant clinically effective as fluoxetine [44] and the systemic blockade of the MAPK pathway in mice produced depressive-like behavior in several animal models of experimental depression as well as inhibits the antidepressant effect of desipramine and fluoxetine in the forced swim test, a main model of depression [45]. On the other hand, the action of BDNF, which has been implicated in the mechanism(s) of action of the antidepressant (see Ref. [46]), is mediated through its high-affinity tyrosine kinase receptor B (TrkB), whose activation is required for antidepressant-like effect [47].

The acute intraventricular administration of IGF-1 produced antidepressant-like effects in mice evaluated in the tail suspension and forced swim tests [48], an effect detected after 3 days of the administration with participation of 5-HT [49]. The antagonism of the mGluR produced antidepressant-like effects in the forced swim test, probably through the intracellular signaling pathways described above [50]. Therefore, there is evidence about the interaction with the estrogens and the serotonergic system on the regulation on the depression disorder not only removing them but also influencing them by the other neurotransmitter systems and other kinds of receptors.

We have already mentioned the difference between the plasmatic estradiol levels during the climacteric stage that is related to the establishment of the depression disease and the antidepressant responses. We have also mentioned that estradiol slows the clearance of 5-HT and at the same time disables the same effect produced by fluvoxamine per se. In this sense during the rat estrous cycle, it has been shown that both estrous and diestrus phases are characterized by low estradiol levels in comparison to the proestrous phase; the fluvoxamine increases the clearance time of 5-HT, but not in the proestrous phase [41]. Rats with 2–3 postovariectomy weeks, it is observed that fluvoxamine increases the clearance time of 5-HT, the same effect caused by the estradiol benzoate treatment. However, the pretreatment with estradiol benzoate blocks the fluvoxamine effect [41].

Additionally evaluated the estradiol effect on the 5-HTT functionality, through time a clearance of the 5-HT, in different ages and postovariectomy time identifying that microinjection of 20pmol of estradiol on CA3 region in the hippocampus to inhibit 5-HTT in young adult rats (4 months age) after 2 weeks from the postovariectomy, but had not effect in middle-age rats (10 months), even with the use of <40 pmol dosage. While fluvoxamine reduces the clearance of 5-HT on rats about 10 months aged with 2 weeks, 4 and 8 months postovariectomy the same way as the 4 months rats [51]. Additionally, they detected that 5 μg/day of estradiol for 2 weeks subcutaneously via implantation of osmotic minipumps produces antidepressant effects on forced swim test on 4-month aged rats but not in 10-month aged rats both with 2 weeks of postovariectomy. Nevertheless the dosage of estradiol for 10 μg/day produces an antidepressant effect after 2 weeks of the postovariectomy procedure, but not at 4 months of postovariectomy in 10-month aged rats. The same dosages produced the same antidepressant effect on older rats (14 months of age) after 2 weeks of postovariectomy. The authors conclude that the lack of an antidepressant effect in estradiol is due to the 4-month hormone withdrawal and not to an age effect. Also in the same study, they reported that 2 weeks of treatment with sertraline, an antidepressant selective serotonin reuptake inhibitors (SSRI), on

rats from 4 to 10 months of age with 2 weeks, 4 months, and 8 months of postovariectomy produce antidepressant effect in the forced swim test. In this study, it is concluded that the age influences the potency of estradiol on the 5-HTT, but its effects were strongly reduced if the period of postovariectomy is longer. On the other hand, the treatment with sertraline inhibited the 5-HTT and produced antidepressant-like effects without affected either by age or length of hormonal depletion [51].

In support to clinics finding about 5-HT2A receptors above mentioned some animal studies it has been observed that the administration of 5-HT2A receptor antagonist, i.e., ketanserin (0.1 mg/kg, i.p., 14 days) produces antidepressant effects in forced swim test and anxiolytic effect in elevated plus-maze test both in the proestrous and estrous phases of estrous cycle, characterized by high concentrations of progesterone and estradiol. In contrast, produces anxiogenic effect in phases with reduce concentrations of estradiol [52]. It is suggested that 5-HT2A receptors play different roles on the modulation of anxiety and depression associated with the alterations of hormonal concentrations during the ovarian cycle. In contrast, ketanserin administered in the same doses (0.1 mg/kg, i.p.) for 7 days in male rats produces an antidepressant-like effect, and together with the antidepressant fluoxetine (5 mg/kg, i.p., 7 days), it potentiates the antidepressant effect in forced swim test [53]. This suggests that the effect of ketanserin on females goes beyond changes in hormonal concentrations, which requires exploration.

Previous searches suggest that different hormonal levels, which vary through different reproductive statuses on women, may cause some changes on serotonergic system. For example, density and potential binding of the 5-HT1A and 5-HT2A receptors, as well as the potential binding of the 5-HTT in different brain structures linked to the mood changes, may contribute to the depression establishment. Those disruptions on the serotonergic system may influence or modify negatively the success of therapeutic response treated with antidepressant drugs or HRT; there is one possibility that must be explored.

5.1. Pharmacological response prediction: 5-HT1A and 5-HT2A receptors

Pharmacological compounds that take action on 5-HT1A receptors such as SSRI are clinically effective antidepressants but require a period of 3–6 weeks of treatment to establish the therapeutic effects [54]. Additionally, 50 to 70% depressed patients respond to the first pharmacological treatment, and less than 40% get a total remission [54]. Combination of SSRI with 5-HT2A receptor antagonist makes the latency period shorter for the establishment of antidepressant effect [55]. This fact suggests that the stimulation of 5-HT1A receptors by SSRI and the inactivity of 5-HT2A receptors, which are part of the serotonin release on limbic areas, produce synergism effect. Therefore, the alteration in the expression of receptors in different brain areas, associated with variations of hormones such as estradiol, mainly in the stages of the climacteric, can influence the pharmacological response to antidepressants.

There are controversial data related to regulatory mechanism, which are exerted to antidepressant treatments on the 5-HT1A and 5-HT2A receptor density. A study developed by

Kranz et al. [56] did not detect differences on the 5-HT1A receptor density on structures such as the hippocampus, the frontal cortex, and the raphe on postmenopausal woman [56]. After the administration of HRT with 17β-valerate ester alone or combined with progesterone, no matter the fact exist, a significant increase of estradiol and progesterone, an effect that has been identified on postmenopausal women [28]. This suggests that plasma concentrations of estradiol that are still elevated in premenopausal women compared to postmenopausal women seem to determine the 5-HT 1A receptor expression on the estrogenic treatment response.

6. Final comments and conclusion

Variations in the levels of ovarian hormones that occur throughout the stages of climacteric and postmenopause severely impact women's mood. The depression is found mainly in the stages with continuous hormonal oscillations like perimenopause and premenopause. However, the relationship between hormonal and serotonergic systems in the climacteric and postmenopausal stages needs to be explored. The neurochemical and neurophysiological modification consequence of the oscillating hormonal levels leads to alterations in the cerebral neurotransmission functioning, mainly on the serotonergic system of the 5-HTT, 5-HT turnover, and 5-HT1A/5-HT2A receptors. This affects the pharmacological response to antidepressant treatments, both with estrogen therapy and with SSRI or tricyclic drugs in the different climacteric and postmenopausal stages.

The limitation on the studies have contributed to the establishment of these hypothesis emerged by the reduced length of women included in the studies and the wide range of ages which is used, because these incorporate women who are in different stages and different reproductive status and also women going through induced oophorectomy postmenopausal on early ages. Also, the lack of quantification of the hormonal levels, principally estradiol, FSH, and the ovarian function markers such as inhibin B, antral follicle count, anti-Müllerian hormone, and the estradiol levels. There is a direct relationship between advanced age and elevated serum basal levels which is associated with poor ovarian response. However, additional studies are needed to support these findings because it should let us categorize effectively those women on their reproductive stage. Thus, it allows us to establish a correct reciprocity between the serotonin changes and evaluated stages.

In addition, some limits in the imaging studies (e.g., PET), which are difficult to correct analysis on small brain structures or markers used, are not always selective to serotonin receptors, principally 5-HT2A receptors. It is also necessary to extend the researches related to serotonin changes on women with some depressant disorder, as major depression on all the reproductive stages, because some recent studies are only used to evaluate the symptomatology improvement on menopause, as somatic, urogenital, or physiologic symptomatology. On the last one, the symptomatology causes low motivation but without depression diagnosis, which limits the exploration of the neurochemical alterations that underlay to the depressive disorder on many different reproductive stages.

There are two areas that have been explored yet; the first one is nonsymptomatic women, thus, probably related to the hormonal levels through the reproductive stages and the correlation with

brain serotonergic function, and also women through oophorectomies on early ages or ovarian failure (both under 40 years old). Women through an abrupt fall on ovarian hormone and some studies point out a high prevalence of depressive disorder longer and severe. Data may contribute to possible genetic factors, biological, psychosocial, and environmental, which are related to the establishment of the depressive disorder on different climacteric and postmenopausal stages.

In conclusion, depression associated to climacteric and postmenopausal stages involves changes in the serotonergic system, which includes an increase in the 5-HT clearance, turnover of 5-HT, and affinity of 5-HTT, as well as increased expression of 5-HT1A and 5-HT2A receptors in different brain regions (i.e., prefrontal cortex and hippocampus). All these changes seem to be a result of the oscillations in the ovarian hormone concentration characteristics of the climacteric and postmenopausal stages.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The present chapter was part of the postdoctoral activities linked to the strengthening of the quality of the national postgraduate that the first author made in the Centro Universitario de los Lagos of the University of Guadalajara with fellowships from the Consejo Nacional de Ciencia y Tecnología (CONACyT, CVU: 210315, SNI: 64200).

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References

[1] World Health Organization. "Depression", in Fact Sheet. 2015. Available online at: http://www.who.int/mediacentre/factsheets/fs369/en/[Accessed 10-September-2015]

[2] Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: The Harvard study of moods and cycles. Archives of General Psychiatry. 2006;**63**(4):385-390. DOI: 10.1001/archpsyc.63.4.385

[3] Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Archives of General Psychiatry. 2004;**61**(1):62-70. DOI: 10.1001/archpsyc.61.1.62

[4] Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Archives of General Psychiatry. 2006;**63**(4):375-382. DOI: 10.1001/archpsyc.63.4.375

[5] Ryan J, Burger HG, Szoeke C, Lehert P, Ancelin ML, Henderson VW, Dennerstein L. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. Menopause. 2009;**16**(3):509-517. DOI: 10.1097/gme.0b013e31818d635f

[6] Stein P, Baldinger P, Kaufmann U, Christina RM, Hahn A, Höflich A, Kranz GS, Savli M, Wadsak W, Mitterhauser M, Winkler D, Kasper S, Lanzenberger R. Relation of progesterone and DHEAS serum levels to 5-HT1A receptor binding potential in pre- and postmenopausal women. Psychoneuroendocrinology. 2014;**46**:52-63. http://dx.doi.org/10.1016/j.psyneuen.2014.04.008

[7] Kugaya A, Epperson CN, Zoghbi S, van Dyck CH, Hou Y, Fujita M, Staley JK, Garg PK, Seibyl JP, Innis RB. Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. The American Journal of Psychiatry. 2003;**160**(8):1522-1524. http://dx.doi.org/10.1176/appi.ajp.160.8.1522

[8] Fedotova IUO, Platonova NA, Sapronov NS. 8-OH-DPAT modulates expression of 5-HT(1A)/5-HT(2A), 17beta-estradiol receptor mRNAs in ovariectomized rats in Porsolt test. Eksperimental'naia i klinicheskaia farmakologiia. 2006;**69**(3):53-57

[9] Yamada N, Araki H, Yoshimura H. Identification of antidepressant-like ingredients in ginseng root (Panax ginseng C.A. Meyer) using a menopausal depressive-like state in female mice: Participation of 5-HT2A receptors. Psychopharmacology (Berl). 2011;**216**(4):589-599. DOI: 10.1007/s00213-011-2252-1

[10] Stein MB, Campbell-Sills L, Gelernter J. Genetic variation in 5HTTLPR is associated with emotional resilience. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2009;**150B**(7):900-906. DOI: 10.1002/ajmg.b.30916

[11] Grochans E, Grzywacz A, Jurczak A, Samochowiec A, Karakiewicz B, Brodowska A, Starczewski A, Samochowiec J. The 5HTT and MAO-A polymorphisms associate with depressive mood and climacteric symptoms in postmenopausal women. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2013;**45**:125-130. DOI: 10.1016/j.pnpbp.2013.05.007

[12] Gressier F, Verstuyft C, Hardy P, Becquemont L, Corruble E. Menopausal status could modulate the association between 5-HTTLPR and antidepressant efficacy in depressed women: A pilot study. Archives of Women's Mental Health. 2014;**17**(6):569-573. DOI: 10.1007/s00737-014-0464-1

[13] Baca-García E, Vaquero C, Diaz-Sastre C, Ceverino A, Saiz-Ruiz J, Fernández-Piquera J, de León J. A pilot study on a gene-hormone interaction in female suicide attempts. European Archives of Psychiatry and Clinical Neuroscience. 2003;**253**:281-285. DOI: 10.1007/s00406-003-0441-6

[14] Freeman EW, Sammel MD, Boorman DW, Zhang R. Longitudinal pattern of depressive symptoms around natural menopause. JAMA Psychiatry. 2014;**71**(1):36-43. DOI: 10.1001/jamapsychiatry.2013.2819

[15] Li RX, Ma M, Xiao XR, Xu Y, Chen XY, Li B. Perimenopausal syndrome and mood disorders in perimenopause: Prevalence, severity, relationships, and risk factors. Medicine (Baltimore). 2016;**95**(32):e4466. DOI: 10.1097/MD.0000000000004466

[16] de Zambotti M, Nicholas CL, Colrain IM, Trinder JA, Baker FC. Autonomic regulation across phases of the menstrual cycle and sleep stages in women with premenstrual syndrome and healthy controls. Psychoneuroendocrinology. 2013;**38**(11):2618-2627. DOI: 10.1016/j.psyneuen.2013.06.005

[17] Almeida OP, Marsh K, Flicker L, Hickey M, Sim M, Ford A. Depressive symptoms in midlife: The role of reproductive stage. Menopause. 2016;**23**(6):669-675. DOI: 10.1097/GME.0000000000000598

[18] Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Rees M, Santoro N, Simoncini T. Menopause. Natural Reviews Disease Primers. 2015;**1**:15004. DOI: 10.1038/nrdp.2015.4

[19] Georgakis MK, Thomopoulos TP, Diamantaras AA, Kalogirou EI, Skalkidou A, Daskalopoulou SS, Petridou ET. Association of age at menopause and duration of reproductive period with depression after menopause: A systematic review and meta-analysis. JAMA Psychiatry. 2016;**73**(2):139-149. DOI: 10.1001/jamapsychiatry.2015.2653

[20] Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: A randomized, controlled trial. Biological Psychiatry. 2004;**55**(4):406-412. http://dx.doi.org/10.1016/j.biopsych.2003.08.011

[21] Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, Brinton EA, Cedars MI, Lobo RA, Merriam GR, Neal-Perry G, Santoro NF, Taylor HS, Black DM, Budoff MJ, Hodis HN, Naftolin F, Harman SM Asthana S. Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS Medicine. 2015;**12**(6):e1001833. DOI: 10.1371/journal.pmed.1001833

[22] Stephenson K, Neuenschwander PF, Kurdowska AK. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women. International Journal of Pharmaceutical Compounding. 2013;**17**(1):74-85

[23] Đoković DD, Jović JJ, Đoković JD, Knežević MŽ, Djukić-Dejanović S, Ristić-Ignjatović DI. Effects of hormone replacement therapy on depressive and anxiety symptoms after oophorectomy. Med Glas (Zenica). 2015;**12**(1):79-85

[24] Morrison JH, Brinton RD, Schmidt PJ, Gore AC. Estrogen, menopause, and the aging brain: How basic neuroscience can inform hormone therapy in women. Journal of Neuroscience. 2006;**26**(41):10332-10348. https://doi.org/10.1523/JNEUROSCI.3369-06.2006

[25] Mantani A, Yamashita H, Fujikawa T, Yamawaki S. Higher incidence of hysterectomy and oophorectomy in women suffering from clinical depression: Retrospective chart review. Psychiatry and Clinical Neurosciences. 2010;**64**(1):95-98. DOI:10.1111/j.1440-1819.2009.02044.x

[26] Jovanovic H, Cerin A, Karlsson P, Lundberg J, Halldin C, Nordström AL. A PET study of 5-HT1A receptors at different phases of the menstrual cycle in women with premenstrual dysphoria. Psychiatry Research. 2006;**148**(2-3):185-193. DOI: 10.1016/j.pscychresns.2006.05.002

[27] Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C. PET imaging of serotonin 1A receptor binding in depression. Biological Psychiatry. 1999;**46**(10):1375-1387. http://dx.doi.org/10.1016/S0006-3223(99)00189-4

[28] Moses-Kolko EL, Price JC, Shah N, Berga S, Sereika SM, Fisher PM, Coleman R, Becker C, Mason NS, Loucks T, Meltzer CC. Age, sex, and reproductive hormone effects on brain serotonin-1A and serotonin-2A receptor binding in a healthy population. Neuropsychopharmacology 2011;**36**:2729-2740. DOI:10.1038/npp.2011.163

[29] Sharp T, Boothman L, Raley J, Queree P. Important messages in the 'post': Recent discoveries in 5-HT neurone feedback control. Trends in Pharmacological Sciences 2007;**28**:629-636. DOI: 10.1016/j.tips.2007.10.009

[30] Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY et al. Serotonin in aging, late-life depression, and Alzheimer's disease: The emerging role of functional imaging. Neuropsychopharmacology. 1998;**18**:407-430. DOI: 10.1016/S0893-133X(97)00194-2

[31] Jovanovic H, Kocoska-Maras L, Rådestad AF, Halldin C, Borg J, Hirschberg AL, Nordström AL. Effects of estrogen and testosterone treatment on serotonin transporter binding in the brain of surgically postmenopausal women—A PET study. NeuroImage 2015;**106**:47-54. DOI: 10.1016/j.neuroimage.2014.11.003

[32] Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: A double-blind, randomized, placebo-controlled trial. Archives of General Psychiatry. 2001;**58**(6):529-534. DOI:10.1001/archpsyc.58.6.529

[33] Liu P, He FF, Bai WP, Yu Q, Shi W, Wu YY, He DJ, Xiao JH, Zheng Y, Liao QP. Menopausal depression: Comparison of hormone replacement therapy and hormone replacement therapy plus fluoxetine. Chinese Medical Journal. 2004;**117**(2):189-194

[34] Berlanga C, Mendieta D, Alva G, del Carmen Lara M. Failure of tibolone to potentiate the pharmacological effect of fluoxetine in postmenopausal major depression. Journal of Women's Health (2002). 2003;**12**(1):33-39. DOI: 10.1089/154099903321154121

[35] D'Haenen H, Bossuyt A, Mertens J, Bossuyt-Piron C, Gijsemans M, Kaufman L. SPECT imaging of serotonin2 receptors in depression. Psychiatry Research Neuroimaging. 1992;**45**:227-237. http://dx.doi.org/10.1016/0925-4927(92)90018-Y

[36] Stockmeier CA. Involvement of serotonin in depression: evidence from postmortem and imaging studies of serotonin receptors and the serotonin transporter Journal of Psychiatric Research. 2003;**37**(5):357-373. DOI:10.1016/S0022-3956(03)00050-5

[37] Attar-Lévy D, Martinot JL, Blin J, Dao-Castellana MH, Crouzel C, Mazoyer B, Poirier MF, Bourdel MC, Aymard N, Syrota A, Féline A. The cortical serotonin2 receptors studied with positron-emission tomography and [18F]-setoperone during depressive illness and antidepressant treatment with clomipramine. Biological Psychiatry. 1999;**45**(2):180-186. http://dx.doi.org/10.1016/S0006-3223(98)00007-9

[38] Li Q, Sullivan NR, McAllister CE, Van de Kar LD, Muma NA. Estradiol accelerates the effects of fluoxetine on serotonin 1A receptor signaling. Psychoneuroendocrinology. 2013;**38**(7):1145-1157. DOI: 10.1016/j.psyneuen.2012.11.005

[39] Kim SW, Park SY, Hwang O. Up-regulation of tryptophan hydroxylase expression and serotonin synthesis by sertraline. Molecular Pharmacology. 2002;**61**(4):778-785. https://doi.org/10.1124/mol.61.4.778

[40] Cone RI, Davis GA, Goy RW. Effects of ovarian steroids on serotonin metabolism within grossly dissected and microdissected brain regions of the ovariectomized rat. Brain Research Bulletin. 1981;**7**:639-644. http://dx.doi.org/10.1016/0361-9230(81)90111-8

[41] Benmansour S, Piotrowski JP, Altamirano AV, Frazer A. Impact of ovarian hormones on the modulation of the serotonin transporter by fluvoxamine. Neuropsychopharmacology. 2009;**34**(3):555-564. DOI: 10.1038/npp.2008.23

[42] Benmansour S, Weaver RS, Barton AK, Adeniji OS, Frazer A. Comparison of the effects of estradiol and progesterone on serotonergic function. Biological Psychiatry. 2012;**71**(7):633-641. DOI: 10.1016/j.biopsych.2011.11.023

[43] Benmansour S, Privratsky AA, Adeniji OS, Frazer A. Signaling mechanisms involved in the acute effects of estradiol on 5-HT clearance. The International Journal of Neuropsychopharmacology. 2014;**17**(5):765-777. DOI: 10.1017/S146114571300165X

[44] Mercier G, Lennon AM, Renouf B, Dessouroux A, Ramaugé M, Courtin F, Pierre M. MAP kinase activation by fluoxetine and its relation to gene expression in cultured rat astrocytes. Journal of Molecular Neuroscience 2004;**24**:207-216. DOI: 10.1385/JMN:24:2:207

[45] Duman CH, Schlesinger L, Kodama M, Russell DS, Duman RS. A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. Biological Psychiatry 2007;**61**:661-670. DOI: 10.1016/j.biopsych.2006.05.047

[46] Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behavioural Pharmacology 2007;**18**:391-418. DOI: 10.1097/FBP.0b013e3282ee2aa8

[47] Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castren E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. Journal of Neuroscience. 2003;**23**:349-357. DOI: 0270-6474/02/220349-09

[48] Malberg JE, Platt B, Rizzo SJ, Ring RH, Lucki I, Schechter LE, Rosenzweig-Lipson S. Increasing the levels of insulin-like growth factor-I by an IGF binding protein inhibitor produces anxiolytic and antidepressant-like effects. Neuropsychopharmacology. 2007;**32**:2360-2368. DOI: 10.1038/sj.npp.1301358

[49] Hoshaw BA, Hill TI, Crowley JJ, Malberg JE, Khawaja X, Rosenzweig-Lipson S, Schechter LE, Lucki I. Antidepressant-like behavioral effects of IGF-I produced by enhanced serotonin transmission. European Journal of Pharmacology. 2008;**594**:109-116. DOI: 10.1016/j.ejphar.2008.07.023

[50] Pomierny-Chamioło L, Poleszak E, Pilc A, Nowak G. NMDA but not AMPA glutamatergic receptors are involved in the antidepressant-like activity of MTEP during the forced swim test in mice. Pharmacological Reports. 2010;**62**(6):1186-1190

[51] Benmansour S, Arroyo LD, Frazer A. Comparison of the antidepressant-like effects of estradiol and that of selective serotonin reuptake inhibitors in middle-aged ovariectomized rats. Frontiers in Aging Neuroscience 2016;**8**:311. DOI: 10.3389/fnagi.2016.00311

[52] Fedotova IuO. Behavioral effects of m-CPP and ketanserine during ovarian cycle in female rats. Eksperimental'naia i klinicheskaia farmakologiia. 2010;**73**(11):6-9

[53] Pilar-Cuéllar F, Vidal R, Pazos A. Subchronic treatment with fluoxetine and ketanserin increases hippocampal brain-derived neurotrophic factor, β-catenin and antidepressant-like effects. British Journal of Pharmacology. 2012;**165**(4b):1046-1057. DOI: 10.1111/j.1476-5381.2011.01516.x

[54] Gaynes BN, Jackson WC, Rorie KD. Major depressive disorder in the primary care setting: Strategies to achieve remission and recovery. The Journal of Family Practice. 2015;**64**(9):S4–S15

[55] Pandey DK, Bhatt S, Jindal A, Gautam B. Effect of combination of ketanserin and escitalopram on behavioral anomalies after olfactory bulbectomy: Prediction of quick onset of antidepressant action. Indian Journal of Pharmacology. 2014;**46**(6):639-643. DOI: 10.4103/0253-7613.144935

[56] Kranz GS, Rami-Mark C, Kaufmann U, Baldinger P, Hahn A, Höflich A, Savli M, Stein P, Wadsak W, Mitterhauser M, Winkler D, Lanzenberger R, Kasper S. Effects of hormone replacement therapy on cerebral serotonin-1A receptor binding in postmenopausal women examined with [carbonyl-^{11}C]WAY-100635. Psychoneuroendocrinology 2014;**45**:1-10. DOI: 10.1016/j.psyneuen.2014.03.004

[57] Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012;**19**(4):387-395. DOI: 10.1097/gme.0b013e31824d8f40

Chapter 6

Use of Phytoestrogens for the Treatment of Psychiatric Symptoms Associated with Menopause Transition

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69541

Abstract

Menopause transition is recognized as a vulnerable period in women life to develop or aggravate symptoms of psychiatric disorders. Several treatments including antidepressants and hormonal restitution with estrogens have been suggested to ameliorate the symptoms. Also, in this period of life is frequent the use of other drugs to treat is also frequent the use of other drugs to treat comorbid pathologies that might even increase the risk of drug-drug interactions. Literature reports that some phytochemicals with estrogenic activity have beneficial effects during menopausal transition without collateral events. This chapter shows evidence about the use of phytoestrogens as an alternative therapy for the treatment of some psychiatric symptoms associated with the menopausal transition. Data derived from preclinical research related to the use of classical phytoestrogens (isoflavones), considering the beneficial effects, as well as adverse events, are discussed. Also, the use of polyphenols and organosulfurate compounds as an alternative for the treatment of anxiety- and depressive-like behavior as well as fibromyalgia is included. A narrative review was conducted using bibliography reporting the use of isoflavones (genistein, daidzein, equol), coumestans or lignans for the reduction of depressive-like or anxiety-like behavior. Furthermore, it is described if the use of this compounds impact in other signs of menopause, i.e. vasomotor and osteoporosis. In addition, due to the high frequency of comorbid pathologies as diabetes mellitus, dyslipidemia or metabolic syndrome with psychiatric disorders, the use of these phytochemicals is discussed.

Keywords: menopause, polyphenols, glycosinolates, phytoestrogens

1. Introduction

With the increase of life expectancy, women potentially spend the last third of their lives in post-menopause. Most of the menopausal women suffer from a variety of symptoms such as hot flashes, night sweats, mood swings, insomnia, vaginal dryness and osteoporosis [1, 2]. Also, the menopause transition could be a vulnerable period to develop some diseases related to mental disorders (i.e., anxiety and depression) and chronic non-degenerative pathologies (metabolic diseases) in addition to menopausal symptoms [3, 4]. This situation implies that women that transit in this period of life could be vulnerable to develop co-morbidities leading to a complex medical management due to the elevated cost and possible pharmacological interactions.

Hormone replacement therapy is considered the first line of treatment for menopause symptoms, mainly vasomotor and night sweats. However, many women refuse it because of their association with increased risk of breast cancer and are considering botanical products or dietary supplements as therapy because they are regarded as safer products [1, 2, 5]. For example, black cohosh is widely employed for hot flashes and mood disorders; others are compounds with estrogenic activity (phytoestrogens) as soy food products, red clover, kudzu, hops, licorice, rhubarb, yam and chasteberry [1].

The use of functional food and nutraceuticals became common to treat menopause symptoms [2]. The term "nutraceutical" combines two words—"nutrient" (a nourishing food component) and "pharmaceutical" (a medical drug). It is defined as "any substance that may be considered a food or part of it that provides medical or health benefits, including the prevention and treatment of diseases." These products include isolated nutrients, dietary supplements and diets genetically engineered "designed" foods, botanical products and processed foods such as cereals, foods and beverages [6]. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease [6]. On the other hand, functional food according to American Dietetic Association, "functional" implies that the food possesses some identified value leading to health benefits, including reducing the risk of adverse effects for a person consuming it [7].

Nutraceuticals and functional food are classified in several manners taken into account their content of specific food, properties (anti-cancer, positive influence on blood lipid profile, anti-inflammatory, osteogenic or bone protective) or chemical structure [6]. Both nutraceuticals and functional food contain active compounds called phytochemicals that confer their properties. Phytochemicals are products of the secondary metabolism of a plant which are biologically active in humans and other animal species playing a greater beneficial role in health more than only nutritional properties. These products are part of the defense system and plants' protection [8], and in humans, they have activity in several systems such as the digestive, immune, cardiovascular, endocrine and central nervous system [6, 8], among others. Also, phytochemicals confer organoleptic properties to vegetables and fruits [8].

Phytochemicals are classified into four groups according to their impact on health [9, 10]:

1. Terpenoids (i.e., carotenoids and phytosterols)
2. Phenols (i.e., flavonoids, phenolic acids, tannins, stilbens and curcuminoids)

http://dx.doi.org/10.5772/intechopen.69541

3. Organosulfurate compounds (i.e., glycosinolates and isothiocyanates)
4. Nitrogen compounds (i.e., alkaloids, betalainas, indol-glycosinolates)

The distribution of phytochemicals' sources could be at the same time diffuse and copious as well as specific depending on the product, for example, carotenoids are frequently found in several products (carrots, tomato, orange, mango, pumpkin, guava), whereeas glycosinolates are found only in cruciferous (broccoli, brussel sprout, cabbage, horseradish, rutabaga) [8]. The concentration of the phytochemical could vary depending on the morphological factors: skin, seed, pulp, peel, leaves, also on agronomic factors: weather, agricultural soil, technical procedure, physiological stress; and postharvest: maturity, processing and storage, among the others [8].

2. Phytochemicals: polyphenols

Polyphenols can be found in a large variety of food mainly of vegetable origin. They constitute the major group of natural compounds known (around 8000 identified) in the plant kingdom [11]. These compounds result of the secondary metabolism of carbon by the acetate-malonate and shikimate pathways. They are characterized by the presence of phenolic structures with a potent antioxidant activity that confers protection to plants against oxidative stress, ultraviolet radiation and other harmful factors of the environment such as pollutants and pathogens [12]. There are a wide variety of polyphenols but, in general, they have been classified into two groups according to their chemicals properties: flavonoids and non-flavonoids (**Figure 1**).

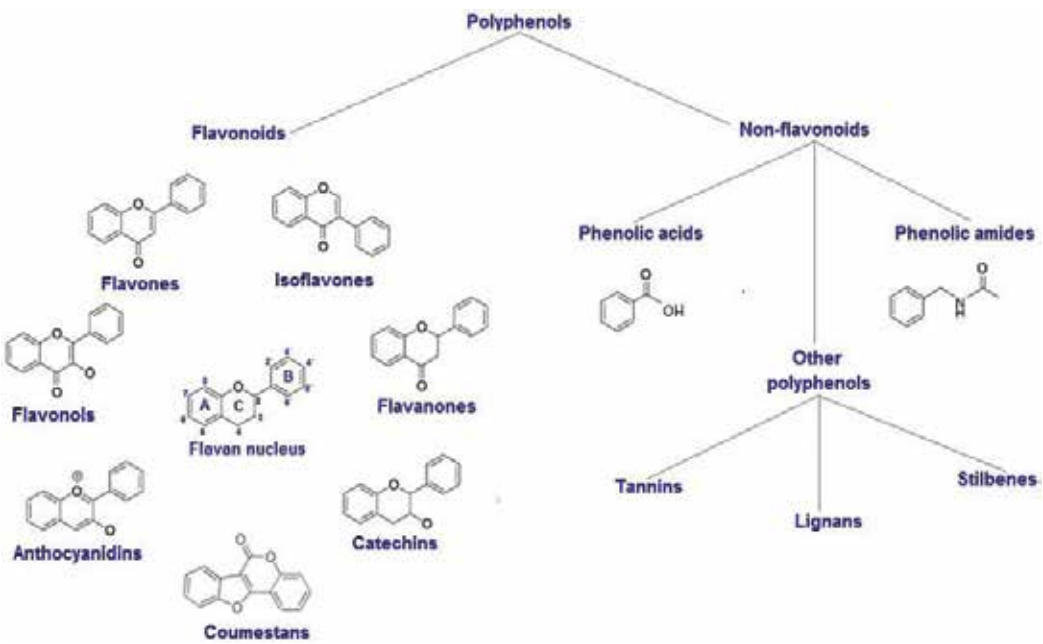

Figure 1. The scheme illustrates the main polyphenols and their division. Phytoestrogens are products of the metabolism of polyphenols: isoflavones and coumenstans are flavonoids, whereas lignans and stilbens are non-flavonoids.

The flavonoid group includes compounds whose structure contains the flavan nucleus (diphenyl propane; C:15: C3, C6, C3), such as anthocyanidins, proanthocyanidins, catechins, flavones, flavonols, flavanones, isoflavones and coumestans (**Figure 1**). The non-flavonoids group includes phenolic acids, phenolic amides and other polyphenols, such as tannins, lignans and stilbene compounds (**Figure 1**). Polyphenols, flavonoids and nonflavonoids have biological importance and are considered as nutraceuticals, not only for their antioxidant effect but also for their beneficial effects on health such as cardiovascular, diabetes and neurodegenerative protection, cancer prevention and anti-infection effect [11].

Recently, it has been determined that some polyphenols, especially isoflavones, flavonols, anthocyanidins, lignans, stilbenes and coumestans, have estrogenic activities, for which they have been denominated as phytoestrogens.

3. Phytoestrogens

Phytoestrogens are non-steroidal compounds that have a unique similarity in molecular weight and the arrangement of aromatic rings with hydroxyl groups to the cyclopentanoperhydrophenanthrene of 17β-estradiol (the most important endogenous estrogen; **Figure 2**).

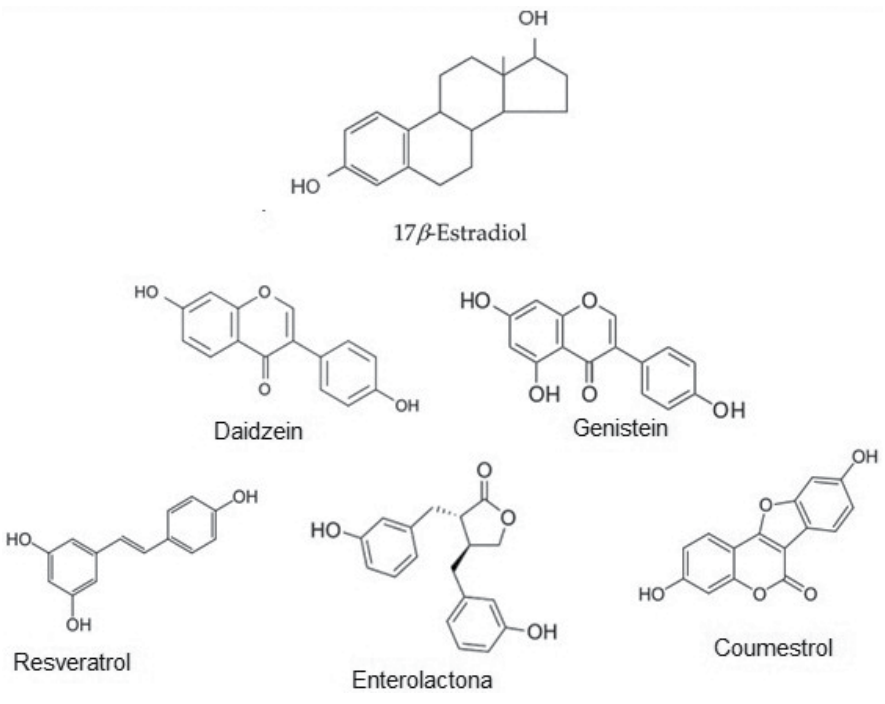

Figure 2. Phytoestrogens. The figure illustrates comparatively the chemical structure of 17β-estradiol and some phytoestrogens. Phytoestrogens are non-steroidal compounds that have a unique similarity in molecular weight and the arrangement of aromatic rings with hydroxyl groups to the cyclopentanoperhydrophenanthrene of 17β-estradiol.

The types of phytoestrogens are isoflavones, lignans, coumestans, ellagitannins and stilbens [13–15]. **Figure 3** shows the main sources of phytoestrogens and the phytochemicals with estrogenic properties. The primary sources of lignans are flaxseed, whole grain cereal and some beverages, such as coffee, tea and wine [15]. For isoflavones are legumens such as soybeans and peanuts, chickpeas and kudzu, lupine, fava, alfalfa, peanuts and chickpeas [15]. In the case of clover alfalfa and soybean sprouts, these are sources of coumestans [13]. Ellagitannins are abundant in fruits, nuts and seeds such as pomegranate, black raspberries, strawberries, walnuts and almonds [16]. The main source of stilbens such as revestratrol is the red wine and peanuts [15].

It is important to note that the beneficial actions of phytoestrogens are mostly given by the estrogenic/anti-estrogenic effect dependent on the resultant concentration of the metabolism

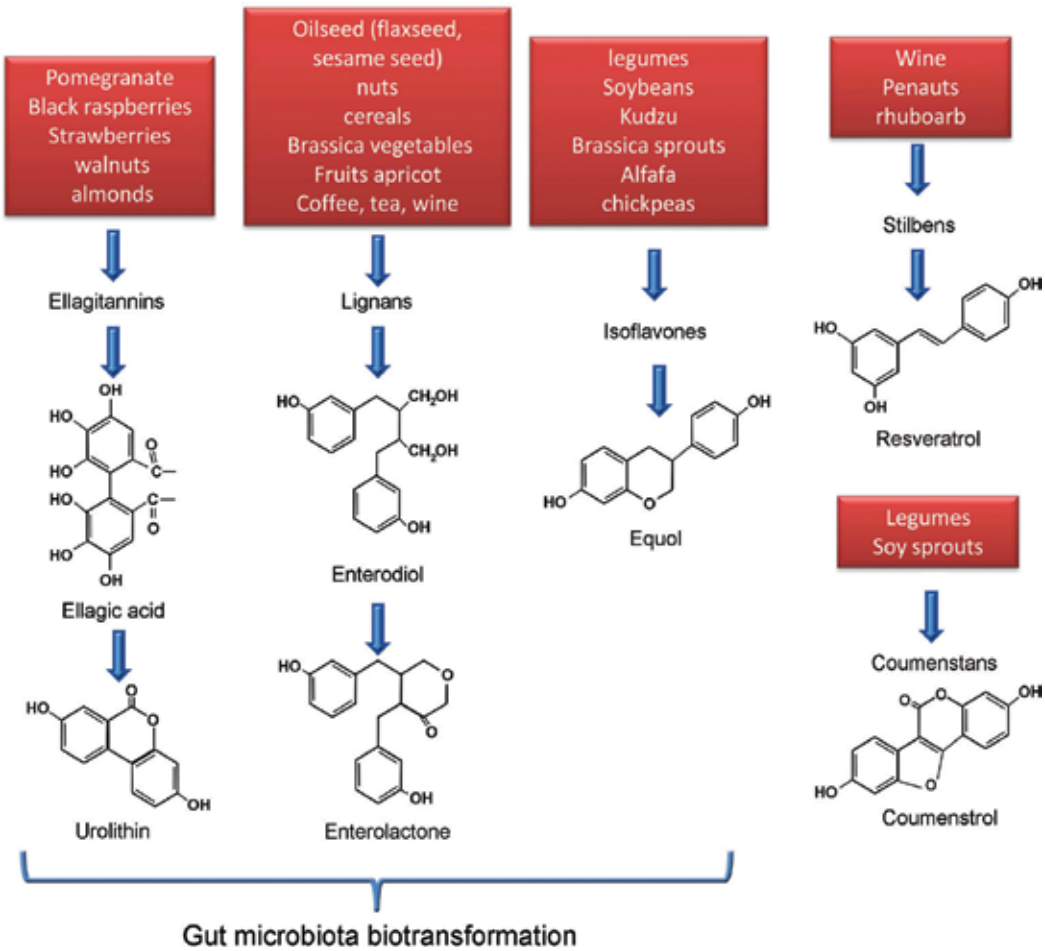

Figure 3. Phytoestrogens and their main food or beverage source. Ellagitannins, lignans and isoflavones require of microbiota biotransformation to release an active compound (urolithins A and B, enteronolactone or Equol, respectively) that produces their estrogen-like effects on different tissues. In contrast, stilbens and coumestans production appears to be independent of microbiota.

of phytoestrogens. It is known that phytoestrogens are mostly as glycosides and that only the aglycone fraction is bio-available to produce biological effects [17]. Some phytoestrogens, such as isoflavones, ellagitannins and lignans, require the action of gut bacterial enzymes to produce equol, urolithins and enterolignans, respectively [16, 18, 19]. These subproducts have more bioavailability and have more estrogenic/anti-estrogenic and anti-oxidant, anti-inflammatory and anti-proliferative activity than their precursors [20]. Furthermore, it is proposed that the biotransformation of isoflavones, ellagitannins and lignans by intestinal microbiota is essential in protection against menopausal symptoms. Also against certain chronic diseases, such as cancer, cardiovascular disease and osteoporosis [15], suggesting that the main discrepancies between a successful treatment versus lack of effect could be explained by the low bioavailability of phytoestrogens [21].

In this line, several reports indicate that coumestans—coumestrol and methoxycoumestrol—show estrogenic activity; the most active compound of isoflavones is daidzein intestinal-derived metabolite equol. However, other products such as genistein, daidzein, glycitein and their respective β-glycosides of genistein and daidzein possess estrogenic activity [13]. Ellagitannins are metabolized to urolithin A and B which showed estrogenic activity [15, 22]. Also, lignans are metabolized in the gut to produce the most estrogenic enterolignans, enterodiol and enterolactone [18].

On the other hand, the chemical similarity between 17β-estradiol and phytoestrogens confers the capability to interact with estrogen receptors (ERs). They produce effects through genomic actions with ERs alpha and beta (α, β) or non-genomic actions via membrane G-protein receptors (GPER) such as GPR30 and mERα and mERβ [23]. These receptors differ in tissue distribution, ligand selectivity and transcriptional processes and, therefore, also differ in their physiological effects on its activation [24–26]. These interactions between phytoestrogens and ERs results on estrogenic and/or anti-estrogenic effects, so that phytoestrogens are considered as selective estrogen receptor modulators (SERMs) [27–29].

Several in vitro assays suggest that phytoestrogens, especially isoflavones, have a significant preference for ERβ rather than for ERα (8- to 40-fold) [30–33]. Some authors explain this preference through steric interaction and through the difference in the attractive potential of hydrogen bonds between the ERs and phytoestrogens, which is higher in ERβ [34]. It is thought, that in some way the beneficial actions of the estrogenic compounds are related to the ERβ, in part because the activation of ERβ has been associated with the anti-proliferative actions of phytoestrogens [35–37].

GPER activation by phytoestrogens has been relatedto cardiovascular, liver enzymatic and neuroprotective actions [35, 38–40]. Some research groups have proposed that the GPR30 also take part in the endocrine disrupting action of phytoestrogens [41]. Phytoestrogens also show high potency in non-genomic responses. Therefore, it is proposed that their binding affinities could be higher for mERs [42] albeit the involvement of these receptors in the phytoestrogens actions is less explored.

As it can be seen phytoestrogens also possess a complex mechanism of actions to exert their properties, for example, the rapid neuroprotective activity of resveratrol against cerebral ischemia

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is mediated by ERα and ERβ, and it is blocked by the estrogen receptor antagonist ICI 182 780 [36]. In contrast, Daidzein protects from excitotoxicity induced by glutamate via ERβ and GPR30 [35].

4. Alternative to the hormone replacement therapy on menopause

4.1. Clinical studies

During menopause, symptoms such as body weight changes, vaginal dryness, hot flushes, sweating, sleep disturbances and loss of bone density may occur, also cognitive disturbance, mood changes and depression episodes that lead women to a poor quality of life [43]. Symptoms could vary in intensity and in some women, they could be debilitating, particularly for those women who have a previous experience of depression and anxiety in addition to vasomotor, insomnia, weight gain and stressful life events [44].

Hormone replacement therapy (HRT) is the first line of treatment followed by the treatment with selective serotonergic reuptake inhibitors antidepressants [2, 45]. Despite their benefits and efficacy for reducing most of the discomforts of menopausal women, the long-term use of HRT has been extremely controversial because of the adverse events associated. These include an increase in the risk of stroke and venous thromboembolism, an increase in endometrial, ovarian and breast cancer, in addition to the regular side effects of HRT such as headaches, weight changes, nausea and pruritus, among others. On the other hand, it has been reported that the adverse effects depend on several factors. Randomized trials have shown that the risk of presenting adverse effects is mainly given in women older than 60 years old, women during postmenopausal and after 5 years of the continued usage of the HRT.

Other therapies including non-pharmacological interventions have been recommended such as psychotherapy to address the psychological symptoms, acupuncture, physical exercise, nutritional interventions, botanical products and folk medicine, among others [44, 46].

Nevertheless, it is increasingly common for women to prefer an alternative therapy based on the intake of therapeutic compounds of natural origin instead. The alternative therapy can be based either on the consumption of food that may provide health benefits beyond nutrition (functional food) or on the administration of compounds isolated from food (nutraceuticals) with the same purpose. In this sense, phytochemicals as phytoestrogens have received much attention because of their particular health benefits which have allowed the emergence of an alternative to HRT.

Most of the therapies used to treat menopausal symptoms have been focusedon alleviating vasomotor and night sweat complaints. One of the most popular therapies is based in the use of black cohosh [33], Valerian and St John's wort [33, 46] due to the lack of estrogenic effects.

Briefly, black cohosh (*Cimicifuga racemosa L. Synonym Actearacemosa L.*) has been used for centuries by native Americans for a variety of women's health issues [33]. It is agreed that black cohosh is not estrogenic and its mechanism of action may involve modulation of the

serotonergic system in a similar manner than antidepressants [1]. This botanical product has been tested in several trials given contradictory results. Indeed, the main effects appear to be related to vasomotor and emotional symptoms [33, 47]. For example, in a multicenter randomized, double-blind, placebo-controlled, parallel group trial, the effect of several doses of black cohosh was tested taking into consideration as a primary outcome the difference in menopausal symptoms (vasomotor, psychological and somatic), assessed by the Kupperman Menopausal Index between baseline and week 12. Secondary efficacy variables were patients' self-assessments of General Quality of Life (QoL), responder rates and safety. Compared to placebo, patients receiving black cohosh showed a significant reduction in the severity of vasomotor and psychological symptoms and improved general QoL in a dose-dependent manner from baseline to endpoint [47]. In contrast, recent clinical trials have reported adverse effects of black cohosh with no significant difference from placebo for relief of hot flashes or improving QoL in Thai women [48].

The phytoestrogens mostly used with documented effects are isoflavones. These compounds obtained from different sources have been used primarily to alleviate vasomotor symptoms, but the results appear not to be consistent on mood complaints. For example, in a metaanalysis (43 randomised controlled trials with 4364 participants) that evaluate the effect of isoflavones from soy and red clover in the treatment of hot flushes and insomnia associated with menopause, no significant difference overall was reported in the incidence of hot flushes between participants taking Promensil (a red clover extract that contains isoflavone biochanin A and formononetin) and those given placebo. In this review, four trials suggested that extracts with high levels (>30 mg/d) of genistein consistently reduced the frequency of hot flushes. Some of these trials found that phytoestrogen treatments alleviated the frequency and severity of hot flushes and night sweats when compared with placebo, but many trials were small and were determined to be at high risk of bias. A strong placebo effect was noted in most trials, with a reduction in frequency ranging from 1 to 59% with placebo. Discrepant results could be related to the amount of isoflavone in the active treatment arm, the severity of vasomotor symptoms or trial quality factors [49].

Other studies tested the effect of red clover and also found controversial results. For example, a trial of 72 women randomly divided between placebo and 40 mg dried red clover daily for 12 weeks showed a significant reduction in menopausal symptoms as measured by the Menopause Rating Scale [50]. In contrast, other clinical trials have not shown a significant difference from placebo, particularly for hot flashes relief [5]. Interestingly, red clover has proestrogens, biochannin A and formonetin, which are metabolized by CYP 450 in the gut and liver in genistein and daidzein [51], suggesting more bioavailability compared with soy products. This could be a reason why the use of red clover appears to be more effective than soy in the clinical trials [52].

Kudzu (*Pueraria lobata* Willd.) Ohwi (Fabaceae) is a traditional Chinese medicine for the treatment of the symptoms of menopause [1]; the major isoflavone in kudzu is puerarin, which is metabolized to daidzein by gut microbiota. Clinical trials with kudzu reported no significant changes in the menopausal complaints compared with control group [53].

Other compounds with estrogenic activity that differ from isoflavones have been tested, for example Hop (*Humulus lupulus* L.) (Cannabaceae). Hop extracts are in some dietary supplements

used for managing menopausal symptoms [54]. The most potent phytoestrogen in hops is the ERα-selective agonist 8-prenylnaringenin (8-PN), which is 100-fold more potent than the ERβ-selective isoflavones genistein and daidzein [33]. Clinical trials suggest positive results of 8-PN in reducing the symptoms of menopause [54] however due to their high affinity to ERα; it is important to evaluate the safety on the endometrium and other hormone-sensitive tissues [33].

Rhubard (*Rheum rhaponticum* L.) (Polygonaceae). Rhubard is a plant used for menopausal symptoms relief in Germany [54]. The extract from roots of rhubard mainly consists of rhaponticin and desoxyrhaponticin, which are converted to the resveratrol-like aglycones rhapontigenin and desoxyrhapontigenin by the microbiome. Rhapontigenin is more active than desoxyrhapontigenin, and it is suggested that P_{450}-catalyzed O-demethylation giving the resveratrol-catechol piceatannol might be responsible for its estrogenic activity [14, 55]. Clinical trials show that the rhubarb extract was effective and successfully decreased the Menopause Rating Scale and increased QoL [56–58].

Flaxseed (*Linum usitatissimum* L.) (Linaceae). Flaxseed is a primary source of lignans that are metabolized by the microbiota into the phytoestrogens, enterolactone and enterodiol [18]. In a randomized placebo-controlled clinical trial (90 women, 1 g/day flaxseed extract), modest but significant effects were observed in self-reporting relief of menopausal symptoms [59]. Nevertheless, a meta-analysis that included randomized clinical trials examining the efficacy of flaxseed for menopausal symptoms, concluded that there is little evidence to support the use of this dietary supplement for menopause or bone health [60].

Another product most employed in South America is maca (*Lepidium meyenii* Walp.) (Brassicaceae), it is used for hormonal balance, especially for menopausal symptoms [54]. Albeit the active phytoestrogen has not been detected, the extract of maca showed estrogenic effect increasing proliferation in MCF-7 cells. A systematic review of clinical trials concluded that evidence of the effectiveness of maca for the relief of menopausal symptoms was limited. However, because of the sample size, the number of trials and the quality of the trials, it is not pertinent to establish definite conclusions about the efficacy and safety [61].

Recently, in a placebo-controlled trial, the efficacy of resveratrol and equol supplementation was tested on menopausal women aged 50–55 years who received 200 mg of fermented soy containing 10 mg of equol and 25 mg of resveratrol (1 tablet/day) during 12 weeks. The primary outcome was the change in score on the Menopause Rating Scale, used to evaluate the severity of age-/menopause-related complaints. Additional outcomes included the Hamilton Rating Scale for Depression (HAM-D) and Nottingham Health Profile (NHP), which were used specifically to assess sleep quality. Treatment was effective to reduce Menopause Rating Scale and HAM-D scores, importantly on work and activity items and with a slight effect on anxiety-related items [62].

According to the results of meta-analyses, there is no enough clinical evidence that supports the use of phytoestrogens as HRT to alleviate all symptoms of menopause. Albeit an improvement in the quality of life is reported. An important issue to consider is the use of standardized phytoestrogens and ethnicity of the women included in the studies since these factors could be crucial to obtain a positive result for those phytoestrogens that require specific microbiota

biotransformation. Promising results are derived from isoflavones and their precursor because of non-adverse effects reported. However, in all cases, more controlled-clinical trials using large samples with women of different ethnicities are required.

4.2. Preclinical studies

In contrast to the clinical studies where the phytoestrogens were evaluated mainly to prevent or alleviate the vasomotor symptoms, in preclinical data, studies were focused on the evaluation of anxious and depressive-like behaviors. Some of the phytoestrogens are considered selective estrogens receptors modulators and are derived from the metabolism of isoflavones. Importantly, most of them showed an affinity for ERβ, characteristic that may explain their effect partially as an antidepressant [63]. However, others showed an affinity for ERα or membrane receptors, making the study of their mechanism of action complex.

Early studies evaluated the effect of dietary phytoestrogens as anxiolytic-like agents [64]. The authors tested the effect of phytoestrogens in the offspring of mothers fed with a dietary soy derived phytoestrogens (600 μg/g) and found a reduction in the anxiety behavior in those animals that were maintained with soy diet when adulthood. Rodents fed with soy also showed less body weight [64]. Unfortunately, in this paper, the authors did not indicate the phytoestrogens bounded with the behavioral effect but reported high levels of equol in plasma, the more active metabolite of isoflavones found in the soy [14].

After that, several doses of a diet rich in phytoestrogens (200 or 600 ppm of phytoestrogens in diet) and equol injections (5 mg/kg) were evaluated in the forced swimming test in rats under different endocrine conditions: intact, ovariectomized and aged rats with natural ovarian failure [65]. Interestingly, the latter group resembles an animal model of "natural menopause" because rats are acyclic, and it is the only report, as far as we know, that evaluate the effect of the isoflavones under this condition. Authors showed that soy diet rich in phytoestrogens and equol produced antidepressant-like effects at the same time that induces a reduction of body weight and white adipose tissue in all endocrine conditions. After the soy-rich diet, high plasmatic levels of genistein, daidzein and equol were detected in those animals that received the highest dose [65]. Unfortunately, the authors did not evaluate anxiety-like behaviors.

In contrast, no effect or anxiogenic effect was reported after a rich isoflavone diet administration [66, 67]. It is important to mention that these data were generated in male rats instead of female rats where more information is needed. Briefly, when a soy-rich diet containing 150 μg/g total isoflavones (daidzein and genistein) was dispensed to young male Lister rats, an anxiogenic effect was reported in the elevated plus-maze and social interaction test. Diet neither affected water intake nor the weight of rats but enhanced the corticosterone and vasopressin stress-response [66], suggesting an increase in sensitivity to stress. The authors explained the apparent discrepancy between results, i.e. Lund and Lephard [64] versus Hartley et al. [66] considering timing and dose used (150 μg/g versus 600 μg/g). Other difference that could be noted is the strain of rats, Long-Evans [64] versus Lister rats [66] and the sex of the rats. The latter is an important issue since Harley et al. [66] used intact male rats, and Lund and Lephard [64] used intact male and female rats finding positive results in anxiety in females but impaired the anxious-like state in males. Further, Patisaul et al. [67]

showed that the administration of a soy-rich (600 μg/g) diet to gonadally intact male rats produced anxiogenic effects. Furthermore, authors tested high (20 mg/kg) and low (3 mg/kg) doses of equol and resveratrol (3 and 20 mg/kg) in two animal models of anxiety in intact male rats. The authors reported that these compounds did not produce any effect after 3 days of treatment and discussed the possibility that the endocrine condition that prevails in males could be a factor to explain the lack of effect [67].

Following this idea, recently it was hypothesized that the role of isoflavones in the regulation of anxiety and depressive-like behavior depends on the endocrine status [68]. To test this hypothesis, the authors evaluated the anxiolytic- and antidepressant-like effect of isoflavone-rich diet (199.4 μg/g) in ovariectomized rats exposed, or not exposed, to estradiol replacement. Data showed that anxiolytic and antidepressant-like effects depend on the endocrine state that prevails during the treatment with isoflavones. In this case, an isoflavone diet combined with estradiol restitution promotes anxiety; in contrast, the same combination promoted an antidepressant-like effect [68]. Unfortunately, authors did not show evidence about the phytoestrogens that could be responsible for the observed effect.

The isoflavone genistein has been evaluated as an antidepressant and anxiolytic compound. This phytoestrogen also showed more affinity for ERβ than ERα [69], and recent reports also suggested that it binds to ERm. Rodríguez-Landa et al. [70]) assayed several doses of this compound (0.25, 0.5 and 1.0 mg/kg, i.p.) after 4 days of administration in Wistar rats with 12-weeks after the elimination of ovaries. This model resembled a long-term period of menopause and was used to evaluate if genistein was able to induce anxiolytic-like effects as hormone replacement therapy after a long-term ovariectomy. In this study, authors showed that genistein was effective in reducing anxiety-like behavior in the black and white model after a long-term postovariectomy. Interestingly, it has been reported that E_2 is ineffective to produce behavioral effects after a long-term ovaries removal [71–73]. Therefore, the results obtained with genistein open the opportunity to use this compound as a restitution therapy. Furthermore, clinical and preclinical studies reported that genistein lacks stimulatory effects in breast and uterus [33]. Genistein also showed antidepressant-like effects in rats subjected to the forced swimming test. In this case, genistein (10 mg/kg) was administered during 14 days to ovariectomized rats and reduction of immobility behavior was observed. Data also indicated that genistein increased dopamine and restored the serotonin levels in the hippocampus at a dose of 10 mg/kg [74]. Interestingly, the effect of this compound was also tested after a subacute administration (i.e., three injections in 24 hours) and no effect was observed. This result suggested a genomic mechanism of action [74].

Another compound with estrogenic properties that has been tested is coumestrol (7,12-dihydrocoumenstan), which is considered a SERM that shows an affinity for the ERβ [69]. This compound was assayed in the forced swimming test and several models of anxiety after systemic (10 μg/kg) and intracerebral administrations (2 μg/μl/slide) to ovariectomized rats. A reduction of depressive-like and anxiety-like behavior was reported after both routes of administration [63]. As it can be noted, coumestrol is effective as an anxiolytic or antidepressant compound in ovariectomized rats; however, it is necessary to evaluate its effect in young intact and acyclic female rats to establish whether the effect of this compound remains even in the presence of ovarian secretion.

Also, secoisolariciresinol (SECO) is a lignan type phytoestrogen mainly found in flaxseed that can be metabolized to enterodiol and enterolactone. This compound was administered (5, 10 and 20 mg/kg, intragastric) during 14 days to ovariectomized mice and tested in two animal models for the screening of antidepressant drugs, the tail suspension test and the forced swimming test. The authors reported an antidepressant-like effect of SECO in both behavioral tests. Furthermore, this compound restored noradrenaline brain levels and increased dopamine and serotonin concentrations without promoting a stimulatory effect on the uterus [75]. An important difference in comparison to other protocols presented here is that SECO was administered immediately after the ovariectomy. Therefore, the restitution started before a real drop in endogenous estrogen levels, suggesting a model of perimenopause rather than a menopause model.

Phytoestrogens appear to promote anxiolytic and antidepressant-like actions in animal models. However, it can be noted that the time, the dose and endocrine state are factors that may condition the effect of these estrogenic compounds. In general, acute interventions are ineffective; most of the reports indicate that more than 3 days are necessary to observe an anxiolytic or antidepressant-like effect. For isoflavones, their effect appears to depend on the time of restitution and the endocrine state of rats. In this line, the fact that their anxiolytic-like effect is observed in ovariectomized or acyclic females but not in intact rats suggests that isoflavones are working as a restitution therapy and the levels of phytoestrogens that are bioavailable after diet administration are enough to induce changes in the respective receptors like a natural estrogen.

5. Alternative sources of phytoestrogens

5.1. *Punica granatum* L. (Lythraceae)

Pomegranate is a fruit native of Western Asia and North Africa. However, it is now cultivated in most of the Mediterranean and North America region [76]. **Table 1** shows the main phytochemicals reported for pomegranate.

Over the last decades, pomegranate and pomegranate extracts have demonstrated to possess several beneficial health effects for which it is considered a functional food. Clinical and preclinical studies have shown that pomegranate has anti-oxidant [77], anti-inflammatory, antitumorigenic, anti-microbial [78], anti-obesity [79], anti-nociceptive [80], neuroprotective [81] and antidepressant-like properties [82–84]. Interestingly, most of the health benefits of pomegranate are attributed to its high content of polyphenols, which represents the 26–30% of the total weight of the fruit [85]. The main polyphenols present in the pomegranate are ellagitannins, such as punicalagin (α and β), and flavonoids such as anthocyanidins, catechins, flavonols and isoflavones [80, 86–88]. Ellagitannins are a type of hydrolyzable tannins with several hexahydroxydiphenoyl (HHDP) groups esterified to sugar moieties. When consumed, ellagitannins are easily hydrolyzed to ellagic acid in the acidic conditions of the gastric juice because of its hydrophilic nature. Therefore, on different portions of the small and large intestine, ellagitannins are transformed by bacterial metabolism to dibenzopyranone compounds called urolithins. These compounds have recently demonstrated to possess estrogenic activity on *in-vitro* assays; this particularity makes pomegranate an excellent source of phytoestrogens [16, 22, 78, 89]. Under this premise, some

Part of the pomegranate	Phytochemicals
Whole	Ellagitannins
	Anthocyanins
	Anthocyanidins
	Catechin
	Proanthocyanidins
Seed and oil	Acid derivates
	Fatty acids
	Triglycerides
	Sterols
	Terpenoids
Peel and pericarp	Ellagitannins
	Gallotannins
	Hydroxybenzoic acids
	Proanthocyanidins
	Flavonols
Leaves	Ellagitannins
	Flavones
	Flavonols
	Flavone glycosides
	Alkaloids
	Acid hydroxybenzoic
	Triterpenoids
	Flavones

Phytochemicals found in several part**s** of pomegranate [79, 80, 86, 87].

Table 1. Phytochemicals found in *Punica granatum* L.

research groups have sought its therapeutic potential for the treatment of symptoms in menopause. In 2012, the therapeutic effect of a 12-week schedule of pomegranate seed oil (PGS) on menopausal symptoms was investigated with a neutral response, i.e., PGS reduced menopausal symptoms, but with no significance, authors remarked the importance of evaluating the PGS for a longer period [90]. Furthermore, a systematic review reported the effect of pomegranate juice in osteoporosis, osteoarthritis, or rheumatoid arthritis. All the studies reported positive effects of pomegranate extract or juice on osteoporosis, osteoarthritis and rheumatoid arthritis [91].

Preclinical studies have reported that the juice of pomegranate reduced menopausal symptoms in animal models by inducing antidepressant-like effects and decreasing bone loss [92].

In our laboratory, an extract of pomegranate in the elevated plus-maze for the screening of anxiolytic action and the forced swimming test for an antidepressant-like effect (unpublished results) was evaluated. This extract has a high content of ellagitannins and previously showed anti-inflammatory and antinociceptive properties [80] After 7 days of intraperitoneal administration, a reduction of anxiety-like behavior was detected and a lack of effect in the forced swimming test. The decrease of anxiety was detected at 1.0 mg/kg (see **Figure 4**). Importantly,

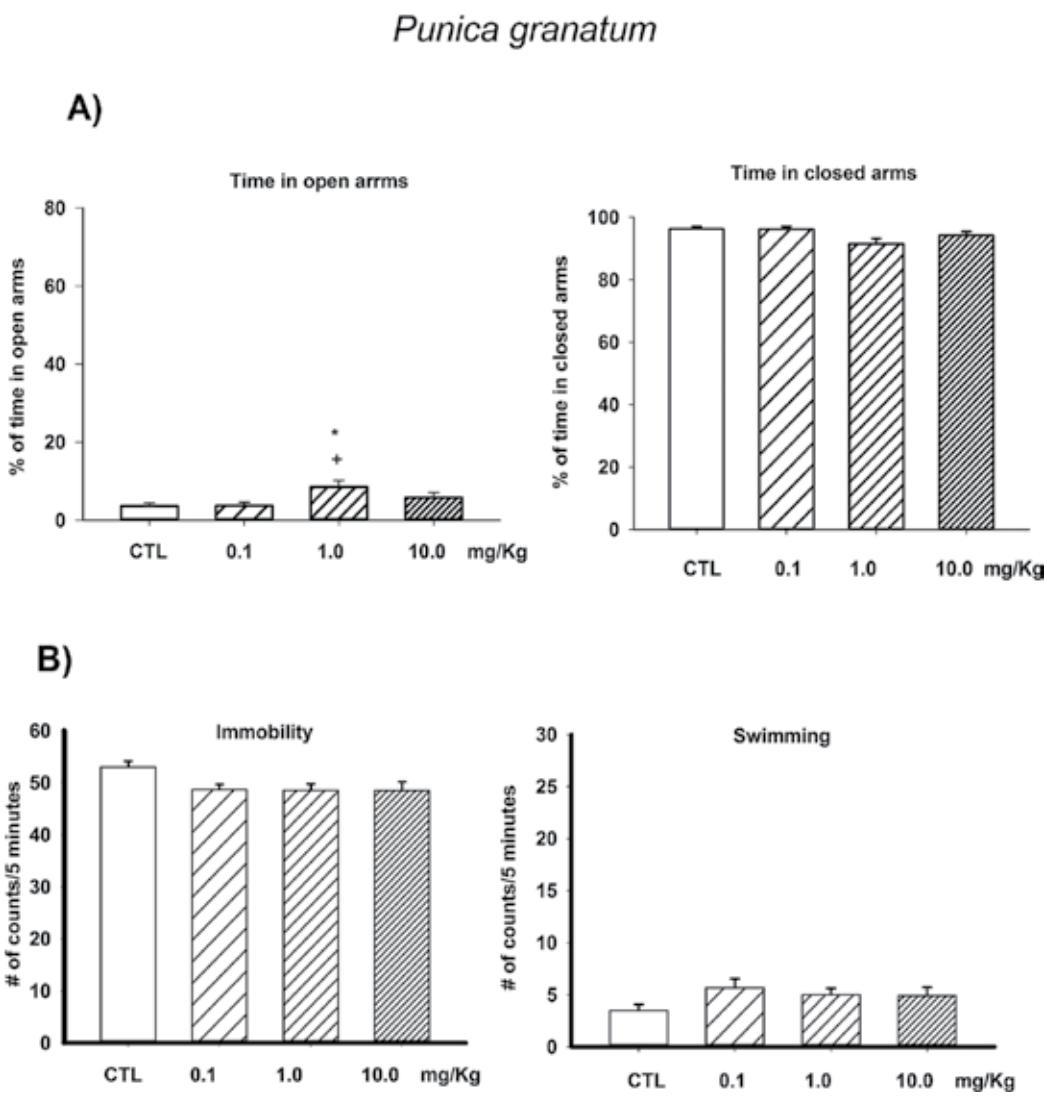

Figure 4. Effect of several doses (0.1, 1.0, 10 mg/kg, i.p) of aqueous extract of pomegranate (*Punica granatum* L.) in the elevated plus-maze (A) and the forced swimming test (panel B) after 7 days of treatment. Pomegranate extract reduced the anxiety-like behavior (panel A) but lacks antidepressant-like effect (B). Data are presented as mean ± SE of 10–12 ovariectomized rats per group. $^{*}p < 0.05$ versus control group; $^{+}p < 0.05$ versus 0.1 mg/kg, One-way-ANOVA followed by Student-Newman Keuls test. Unpublished results.

http://dx.doi.org/10.5772/intechopen.69541

the fact that the administration route was intraperitoneal suggests that other phytochemicals more than ellagitannins, which require of microbiota transformation, could be present in the extract. Future experiments may contribute to elucidate the phytochemical bounded in the anxiolytic effect of pomegranate.

5.2. *Brassica oleraceae* var. *italica*

Broccoli (*Brassica oleracea* var. *italica* Plenck) belongs to the Brassicaceae of cruciferous family where cabbage, brussels sprouts and radish can also be found [93]. It is native to the Anatolian peninsula and now is widely cultivated in other parts of the world. The phytochemical content of broccoli is shown in **Table 2**. As it can be seen, broccoli is also a source of important polyphenols, and consequently, phytoestrogens since in its composition, it can be detected quercetin, kaempferol, daidzein, antocyanins [93, 94], coumestans and lignans [45, 95].

Phytochemicals	Unity	Broccoli
β-Carotene	UI	318.56
Zeaxanthin	UI	22
Lutein	μg	1123.76
β-Cryptoxanthin	UI	0.88
Quercetin	mg	2.2
Kaempferol	mg	0.008
Myricetin	mg	3.5288
Daidzein	mg	0.0352
Anthocyanin	μg	0.01
Lignans	μg	0.528
Glucoiberin	μmol	145.2
Glucoraphanin	μmol	646.8
Progoitrin	μmol	80.15
Glucoalyssin	μmol	69.78
Gluconapin	μmol	22.88
Glucobrassicanapin	μmol	23.707
Gluconasturtiin	μmol	9.52
Glucobrassicin	μmol	308
Neo-glucobrassicin	μmol	84.48
Chlorophyll (A)	mg	0.88
Chlorophyll (B)	mg	0.748

Phytochemicals of Broccoli. Data are expressed as UI, mg, μg or μmol per 98 g of dried sample [96–117].

Table 2. Phytochemicals in different parts of *Brassica oleraceae*.

Broccoli is also a source of a potent anti-oxidant and anti-inflammatory compound called sulforaphane (1-isothiocyanato-4-methylsulfinylbutane) which is an organosulfur compound [118]. Several reports indicated that this compound might prevent depressive-like behavior induced by the inflammatory process. For example, acute sulforaphane at 3–30 mg/kg and glucorophanin (glucosinolate precursor of sulforaphane) in the diet were tested in male C57BL/6 mice. In this case, it was to determine whether these compounds were able to prevent the onset of depression-like behavior after an induction of inflammation by lipopolysaccharide administration [118]. In this chapter, authors also evaluate the effect of sulforaphane on brain-derived neurotrophic factor (BDNF) levels, synaptogenesis protein and dendritic spine density in the brain. The results showed that sulforaphane prevents the increase of TNF-α, IL-10 and microglia activation blocking the inflammation process at the same time that decreased the depressive-like behavior evaluated by two behavioral test. Interestingly, sulforaphane also reverses the reduction of BDNF expression and dendritic spines induced by inflammation process [118].

In another study, the effect of sulporaphane and glucorophaninwas tested on depressive-like behavior after repeated social defeat stress using Nrf2 knock-out mice. Nrf2 is a transcription factor keap-1 system that plays a role in the inflammation and evidence has shown that both peripheral and central inflammation plays a crucial role in the pathophysiology of depression [119]. The administration of diet rich in sulforaphane and glucorophanin prevented the depressive-like behavior during adulthood; further authors showed that dietary intake of SFN-rich food during juvenile stages and adolescence could confer stress resilience in adulthood [119].

Contrasting results have also been reported, for example, Balb/c mice received sulforaphane (50 mg/kg) previous to the injection of lipopolysaccharide afterward sickness behavior (an animal model of depression), and the proinflammatory response was evaluated in the hippocampus. The authors reported that sulforaphane administration prevented the induction of pro-inflammatory mediators (IL-b; IL-6, Cybb, INOS) but did not improve sickness behavior [120, 121]. Therefore, the use of sulforaphane to prevent depression-like behavior is inconclusive.

As far as we know, there is no information about the use of sulforaphane or glucorophanin in animal models of menopause. However, it has been suggested that the advantage of broccoli consumption is that some phytochemicals promote the conversion of 16-a-hydroxyestrone to 2-hydroxyestrone, the first is a carcinogenic metabolite that has been linked to breast cancer risk whereas the latter product does not exhibit estrogenic properties in breast tissue. Apparently, the ingestion of broccoli sprouts could be a good strategy for the treatment of menopause symptoms [2, 122, 123].

In our laboratory, several doses (0.1, 1.0, 10 mg/kg, i.p) of an extract of broccoli were evaluated for its anxiolytic and antidepressant-like effects after 7 days of administration to 3-week post-ovariectomized rats. The results indicated an anxiolytic—but not antidepressant-like effect (**Figure 5**, unpublished results). The phytochemical involved in this action is unknown and studies to reveal it are running.

The fact that sulforaphane exerts anti-inflammatory properties and that according to the aetiology of depression, the inflammatory process plays a major role in its aetiology, the consumption of food or nutraceuticals with sulforaphane could be suitable.

http://dx.doi.org/10.5772/intechopen.69541

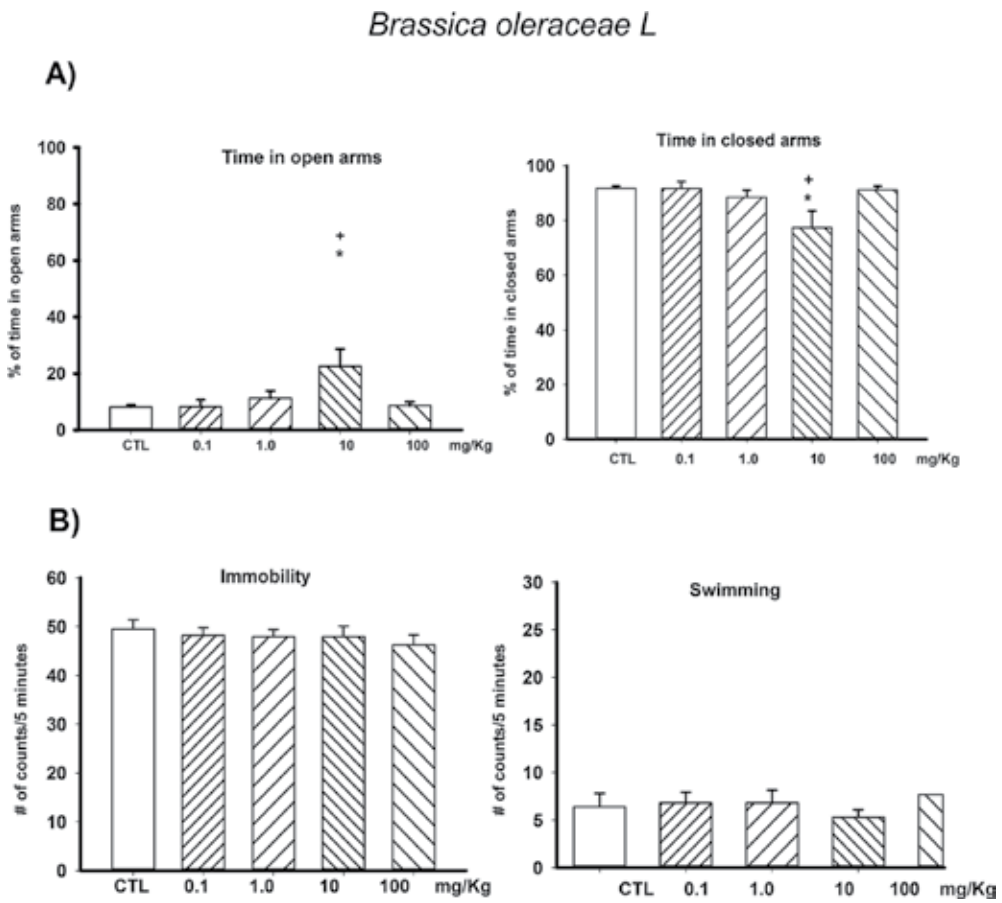

Figure 5. Effect of several doses (0.1, 1.0, 10 and 100 mg/kg, i.p) of aqueous extract of broccoli (*Brassica oleraceae* L) in the elevated plus-maze (A) and the forced swimming test (B) after 7 days of treatment. Broccoli extract reduced the anxiety-like behavior (A) but lacks antidepressant-like effect (B). Data are presented as mean ± SE of 10–12 ovariectomized rats per group. *$p < 0.05$ versus control group; +$p < 0.05$ versus 0.1 mg/kg, One way-ANOVA followed by Student-Newman Keuls test. Unpublished results.

6. Comorbidity in menopause and alternative medicine

Fibromyalgia (FM) is a chronic, generalized pain syndrome that affects the musculoskeletal system [124]. It is characterized not only by a widespread pain observed due to the presence of multiple tender points but also by depressive behavior, fatigue and sleep disturbances without any structural or inflammatory cause [125, 126]. Studies have consistently demonstrated a female predominance of this disease [127] with a major frequency in pre- and post-menopause condition supporting that an abrupt decline or a reduced time of exposure to ovarian hormones may contribute to FM [128].

Although FM is not an inflammatory disease, it is known that a neuroinflammation process can occur, which is described as an increase in the production of interleukins at the central

nervous system level, such as IL-1β, IL-6, IL-8, IL-10 and TNF-α, and not at the peripheral level [129]. To date, it has not been possible to establish whether their elevated levels are associated with the painful process in FM since these have also been observed in patients with depression and sleep disorders [130]. The neuroendocrine alterations observed are usually at the level of the hypothalamic-pituitary-adrenal axis where there is hyperactivation, and it has been related to deficient levels of hormones [131] that could be part of the reasons of a major frequency in menopause [128].

As it was mentioned, anthocyanidins belong to the flavonoid group of plant-derived chemicals, which have been commonly used for the treatment of chronic diseases. One randomized clinic test was done to evaluate the efficacy of this compounds (40, 80 and 120 mg/day) in the treatment of FM compared with a placebo group. The evaluation had duration of 52 weeks with each treatment given for 12 weeks, preceded by a 4-week baseline period. Authors conclude that anthocyanidins showed small but significant benefits at a dosage of 80 mg/day in the treatment of primary FM, mainly in the sleep disturbance in the presence of minor adverse effects like indigestion or nausea [132].

Chronic fatigue syndrome is also comorbid linked to early menopause and FM since it involves the muscular, nervous, hormonal and immune systems; it is often misdiagnosed as depression [133]. Isoflavones (daidzein and genistein) were capable of reversing alterations like chronic fatigue syndrome in an experimental model in mice suggesting their protective effect in this neuroimmune-endocrine disease [134].

7. Concluding remarks

1. Clinical reports show inconsistent results about the use of phytoestrogens effectiveness to treat vasomotor and psychiatric disorders associated with menopause. The biotransformation by microbiota to deliver the main active compounds appears to be fundamental to observe positive effects.
2. Preclinical data show that the effect of phytoestrogens depends on the time of administration as well as the endocrine state of rats, suggesting that these factors could also contribute to explain the inconsistency between results observed in humans.
3. More studies are necessary to evaluate if the same phytoestrogen can induce both anxiolytic- and antidepressant-like action and if their effect depends on the endocrine state.
4. Clinical and preclinical studies indicated that the use of phytoestrogens is safe due to the high antioxidant activity. However, meta-analysis studies are inconclusive. Therefore, phytoestrogens as restitution therapy should be monitored.
5. Functional food and nutraceuticals are an important source of a wide variety of phytoestrogens.

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References

[1] Hajirahimkhan A, Dietz BM, Bolton JL. Botanical modulation of menopausal symptoms: mechanisms of action? Planta Medica. 2013;**79**:538-553

[2] Comhaire FH, Depypere HT. Hormones, herbal preparation and nutraceuticals for better life after the menopause: Part II. Climateric. 2015;**18**:364-371

[3] Parry BL. Perimenopausal depression. The American Journal of Psychiatry. 2008;**165**: 23-27

[4] Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen, and cognitive aging: The timing hypothesis. Neurodegener Ative Diseases. 2009;**7**:163-166

[5] Geller SE, Studee L. Botanical and dietary supplements for menopausal symptoms: What works, what does not. Journal of Women's Health. 2005;**14**:634-649

[6] Wildman R, Kelley M. Nutraceuticals and functional foods. In: Wildman R, editor. Handbook of Nutraceutical and Functional Foods. 2nd ed. New York: CRC Press, Taylor & Francis Group; 2006. Chapter 1

[7] American Dietetics Association. Position of the American Dietetic Association: Functional foods position statement. Journal of the American Dietetic Assocciation. 2004; **104**:814-826

[8] Gonzalez-Laredo R, Rocha-Guzmán E, Gallegos Infante JA. Fitoquímicos en los alimentos. In: Álvarez E, editor. Antioxidantes en alimentos y salud. México D.F.: Clave; 2012. pp. 133-154. Cap. 6

[9] Rodríguez EB, Flavier ME, Rodríguez-Amaya DB, Amaya-Farfán J. Phytochemicals and funcrional foods. Currem Situation and prospect for developing countries. Seguridad Alimentaria en Nutrició, Campinas. 2006;**13**:1-22

[10] Crozier AM, Clifford N, Ashihara H. Plant Secundary Metabolites. Occurrence, Structure and Role in the Human Diet. Oxford, RU: Blackwell; 2006

[11] Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients. 2010;**2**:1231-1246

[12] Duda-Chodak A, Tarko T, Satora, P, Sroka P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. European Journal of Nutrition. 2015;**54**:325-341

[13] Philp HA. Hot flashes—a review of the literature on alternative and complementary treatment approaches. Alternative Medicine Review. 2003;**8**:284-302

[14] Gaya P, Medina M, Sánchez-Jiménez A, Landete JM. Phytoestrogen metabolism by adult human gut microbiota. Molecules. 2016;**21**:1034. DOI: 10.339.

[15] Landete JM, Arqués J, Medina M, Gaya P, de Las Rivas B, Muñoz R. Bioactivation of phytoestrogens: Intestinal bacteria and health. Critical Review in Food Science and Nutrition. 2016;**56**:1826-1843

[16] Landete JM. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. Food Research International. 2011;**44**(5): 1150-1160

[17] Cederroth CR, Nef S. Soy, phytoestrogens and metabolism: A review. Molecular and Cellular Endocrinology. 2009;**304**:30-42

[18] Landete JM. Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health. Food Research International. 2012;**46**:410-424

[19] Setchell KDR, Brown NM, Desai PB, Zimmer-Nechimias L, Wolfe B, Jakate AS, Heubi JE. Bioavailability, disposition, and dose-response effects of soy isoflavones when consumed by healthy women at physiologically typical dietary intakes. The Journal of Nutrition. 2003;**133**(4):1027-1035

[20] Seeram NP, Aronson WJ, Zhang Y, Henning SM, Moro A, Lee RP, Sartippour M, Harris DM, Rettig M, Suchard MA, Pantuck AJ, Belldegrun A, Heber D. Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. Journal Agricultural and Food Chemestry. 2007;**55**:7732-7737

[21] Landete JM, Arqués J, Medina M, Gaya P, de Las Rivas B, Muñoz R. Bioactivation of phytoestrogens: Intestinal bacteria and health. Critical Reviewsin Food Scienceand Nutrition. 2015;**56**:1826-1843

[22] Larrosa M, González-Sarrías A, García-Conesa MT, Tomás-Barberán F, Espín JC. Urolithins, ellagic acid-derived metabolites produced by human colonic microflora, exhibit

estrogenic and antiestrogenic activities. Journal of Agricultural and Food Chemistry. 2006;**54**:1611-1620

[23] Watson CS, Bulayeva NN, Wozniak AL, Finnerty CC. Signaling from the membrane via membrane estrogen receptor-alpha: Estrogens, xenoestrogens, and phytoestrogens. Steroids. 2005;**70**(5-7 SPEC. ISS.):364-371

[24] Paterni I, Granchi C, Katzenellenbogen J, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): Subtype-selective ligands and clinical potential. Steroids. 2014;**90**:13-29

[25] Prossnitz ER, Barton M. The G-protein-coupled estrogen receptor GPER in health and disease. Nature Reviews Endocrinology. 2011;**7**:715-726

[26] Jeng YJ, Kochukov MY, Watson CS. Membrane estrogen receptor-alpha-mediated non-genomic actions of phytoestrogens in GH3/B6/F10 pituitary tumor cells. Journal of Molecular Signaling. 2009;**4**:2

[27] Díaz-Yamal I, Munévar-Vega L. Fitoestrógenos: Revisión de tema Phytoestrogens : Atopicreview. Rev. Colombiana de Obstetricia y Ginecología. 2009;**60**(3):274-281

[28] Moreira AC, Silva AM, Santos MS, Sardão VA. Phytoestrogens as alternative hormone replacement therapy in menopause: What is real, what is unknown. Journal of Steroid Biochemistry and Molecular Biology. 2014;**143**:61-71

[29] Patisau HB, Jefferson W. The pros and cons of phytoestrogens. Frontiers in Neuroendocrinology. 2010;**31**(4):400-419. DOI: 10.1016/j.yfrne.2010.03.003.

[30] Nikov GN, Hopkins NE, Boue S, Alworth WL. Interactions of dietary estrogens with human estrogen receptors and the effect on estrogen receptor-estrogen response element complex formation. Environmental Health Perspectives. 2000;**108**(9):867-872. DOI: 10.1289/ehp.00108867

[31] Zand RS, Jenkins DJ, Diamandis EP. Steroid hormone activity of flavonoids and related compounds. Breast Cancer Research and Treatment. 2000;**62**:35-49

[32] Zava DT, Blen M, Duwe G. Estrogenic activity of natural and synthetic estrogens in human breast cancer cells in culture. Environmental Health Perspectives. 1997;**105**(Suppl):637-645. DOI: 10.1289/ehp.97105s3637

[33] Dietz BM, Hajirahimkhan A, Dunlap TL, Bolton JL. Botanicals and their bioactive phytochemicals for women's health. Pharmaceuticals Reviews. 2016;**68**:1026-1073

[34] Manas ES, Xu ZB, Unwalla RJ, Somers WS. Understanding the selectivity of genistein for human estrogen receptor-alpha using X-ray crystallography and computational methods. Structure. 2004;**12**:2197-2207. DOI: 10.1016/j.str.2004.09.015

[35] Kajta M, Rzemieniec J, Litwa E, Lason W, Lenartowicz M, Krzeptowski W, Wojtowicz AK. The key involvement of estrogen receptor β and G-protein-coupled receptor 30 in the neuroprotective action of daidzein. Neuroscience. 2013;**238**:345-360

[36] Saleh MC, Connell BJ, Saleh TM. Resveratrol induced neuroprotection is mediated via both estrogen receptor subtypes, ER(α) and ER(β). Neuroscience Letters. 2013;**548**:217-221

[37] Vargas KG, Milic J, Zaciragic A, Wen K, Jaspers L, Nano J, Franco OH. The functions of estrogen receptor beta in the female brain: A systematic review. Maturitas. 2016. DOI: 10.1016/j.maturitas.2016.05.014

[38] Lin AHY, Leung GPH, Leung SWS, Vanhoutte PM, Man RYK. Genistein enhances relaxation of the spontaneously hypertensive rat aorta by transactivation of epidermal growth factor receptor following binding to membrane estrogen receptors-alpha and activation of a G protein-coupled, endothelial nitric oxide synthase-dependent pathway. Pharmacological Research. 2011;**63**(3):181-189

[39] Lindsey SH, Chappell MC. Evidence that the G protein-coupled membrane receptor GPR30 contributes to the cardiovascular actions of estrogen. Gender Medicine. 2011; **8**(6):343-354

[40] Pinto Patricia I, Estevao S, Dulce M, Andrade A, Santos, Soraia P, Deborah M. Tissue responsiveness to estradiol and genistein in the sea bass liver and scale. Journal of Steroid Biochemistry and Molecular Biology. 2016;**158**:127-137. ISSN: 1879-1220

[41] Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. Journal of Steroid Biochemistry and Molecular Biology. 2006;**102**(1-5 SPEC. ISS.):175-179

[42] Watson CS, Alyea RA, Cunningham KA, Jeng YJ. Estrogens of multiple classes and their role in mental health disease mechanisms. International Journal Women's Health. 2010;**2**:153-166

[43] Roberts H, Hickey M. Managing the menopause: An update. Maturitas. 2016;**86**:53-58

[44] Brando AR, Shivakumar G, Freeman M. Perimenopausal depression. Hormones, antidepressants, psychotherapy-what would you recommend? Current Psychiatry. 2008; **7**:39-50

[45] Poluzzi E, Piccinni C, Raschi E, Rampa A, Recanatini M, De Ponti F. Phytoestrogens in postmenopause: The state of the art from a chemical, pharmacological and regulatory perspective. Current Medicinal Chemistry. 2014;**21**:417-436

[46] Taylor M. Alternative medicine and the perimenopause an evidence-based review. Obstetrics & Gynecology Clinics of North America. 2002;**29**:555-573

[47] Schellenberg R, Saller R, Hess L, Melzer J, Zimmermann C, Drewe J, Zahner C. Dose-Dependent Effects of the *Cimicifuga racemosa* extract Ze 450 in the treatment of climacteric complaints: A randomized, Placebo-Controlled Study. Evidence-Based Complement Alternative Medicine. 2012;**2012**:260-301

[48] Tanmahasamut P, Vichinsartvichai P, Rattanachaiyanont M, Techatraisak K, Dangrat C, Sardod P. *Cimicifuga racemosa* extract for relieving menopausal symptoms: A randomized controlled trial. Climacteric. 2015;**18**:79-85

[49] Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database of Systematic Reviews. 2013;**12**(12):CD001395

[50] Shakeri F1, Taavoni S, Goushegir A, Haghani H. Effectiveness of red clover in alleviating menopausal symptoms: A 12-week randomized, controlled trial. Climacteric. 2015; **18**:568-573

[51] Tolleson WH, Doerge DR, Churchwell MI, Marques MM, Roberts DW. Metabolism of biochanin A and formononetin by human liver microsomes in vitro. Journal of Agricultural and Food Chemistry. 2002;**50**:4783-4790

[52] Thomas AJ, Ismail R, Taylor-Swanson L, Cray L, Schnall JG, Mitchell ES, Woods NF. Effects of isoflavones and amino acid therapies for hot flashes and co-occurring symptoms during the menopausal transition and early postmenopause: A systematic review. Maturitas. 2014;**78**:263-276

[53] Ulbricht C, Bryan JK, Costa D, Culwell S, Giese N, Isaac R, Nummy K, Pham T, Rapp C, Rusie E, Weissner W, Windsor RC, Woods J, Zhou S. An Evidence-Based systematic review of Goji (*Lycium* spp.) by the natural standard research collaboration. Journal of Dietary Supplements. 2015;**12**:184-240

[54] Taylor M. Complementary and alternative approaches to menopause. Endocrinology Metabolism Clinics of North America. 2015;**44**:619-648

[55] Wober J, Möller F, Richter T, Unger C, Weigt C, Jandausch A, Zierau O, Rettenberger R, Kaszkin-Bettag M, Vollmer G. Activation of estrogen receptor-beta by a special extract of *Rheum rhaponticum* (ERr 731), its aglycones and structurally related compounds. Journal of Steroid Biochemistry and Molecular Biology. 2007;**107**:191-201

[56] Heger M, Ventskovskiy BM, Borzenko I, Kneis KC, Rettenberger R, Kaszkin-Bettag M, Heger PW. Efficacy and safety of a special extract of *Rheum rhaponticum* (ERr 731) in perimenopausal women with climacteric complaints: A 12-week randomized, double-blind, placebo-controlled trial. Menopause. 2006;**13**:744-759

[57] Kaszkin-Bettag M, Beck S, Richardson A, Heger PW, Beer AM. Efficacy of the special extractERr 731 from *Rhapontic rhubarb* for menopausal complaints: A 6-month open observational study. Alternative Therapies in Health Medicine. 2008;**14**:32-38

[58] Hasper I, Ventskovskiy BM, Rettenberger R, Heger PW, Riley DS, Kaszkin-Bettag M. Long-term efficacy and safety of the special extract ERr 731 of *Rheum rhaponticum* in perimenopausal women with menopausal symptoms. Menopause. 2009;**16**:117-131

[59] Colli MC, Bracht A, Soares AA, de Oliveira AL, Bôer CG, de Souza CG, Peralta RM. Evaluation of the efficacy of flaxseed meal and flaxseed extract in reducing menopausal symptoms. Journal of Medicine Food. 2012;**15**:840-845

[60] Dew TP, Williamson G. Controlled flax interventions for the improvement of menopausal symptoms and postmenopausal bone health: A systematic review. Menopause. 2013;**20**:1207-1215

[61] Lee MS, Shin BC, Yang EJ, Lim HJ, Ernst E. Maca (Lepidium meyenii) for treatment of menopausal symptoms: A systematic review. Maturitas. 2011;**70**:227-233

[62] Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. Maturitas. 2017;**96**:77-83

[63] Walf AA, Rhodes ME, Frye CA. Antidepressant effects of ERbeta-selective estrogen receptor modulators in the forced swim test. Pharmacology Biochemistry and Behavior. 2004;**78**:523-529

[64] Lund TD, Lephart ED. Dietary soy phytoestrogens produce anxiolytic effects in the elevated plus-maze. Behavioural Brain Research. 2001;**913**:180-184

[65] Blake C, Fabick KM, Setchell KD, Lund TD, Lephart ED. Neuromodulation by soy diets or equol: Anti-depressive & anti-obesity-like influences, age- & hormone-dependent effects. BMC Neuroscience. 2011;**16**:12-28

[66] Hartley DE, Edwards JE, Spiller CE, Alom N, Tucci S, Seth P, Forsling ML, File SE. The soy isoflavone content of rat diet can increase anxiety and stress hormone release in the male rat. Psychopharmacology (Berl). 2003;**167**:46-53

[67] Patisaul HB, Burke KT, Hinkle RE, Adewale HB, Shea D. Systemic administration of diarylpropionitrile (DPN) or phytoestrogens does not affect anxiety-related behaviors in gonadally intact male rats. Hormones and Behavior. 2009;**55**:319-328

[68] Russell AL, Grimes JM, Larco DO, Cruthirds DF, Westerfield J, Wooten L, Keil M, Weiser MJ, Landauer MR, Handa RJ, Wu TJ. The interaction of dietary isoflavones and estradiol replacement on behavior and brain-derived neurotrophic factor in the ovariectomized rat. Neuroscience Letters. 2017;**640**:53-59

[69] Kuiper GG, Gustafsson JA. The novel estrogen receptor-beta subtype: Potential role in the cell- and promoter-specific actions of estrogens and anti-estrogens. FEBS Letters. 1997;**410**:87-90

[70] Rodríguez-Landa JF, Hernández-Figueroa JD, Hernández-Calderón BC, Saavedra M. Anxiolytic-like effect of phytoestrogen genistein in rats with long-term absence of ovarian hormones in the black and white model. Progress in Neuropsychopharmacology & Biological Psychiatry. 2009;**33**:367-372

[71] Estrada-Camarena E, Lopez-Rubalcava C, Hernandez-Aragon A, Mejia-Mauries S, Picazo O. Long-term ovariectomy modulates the antidepressant-like action of estrogens, but not of antidepressants. Journal of Psychopharmacology. 2011;**25**:1365-1377

[72] De Chaves G, Moretti M, Castro AA, Dagostin W, et al. Effects of long term ovariectomy on anxiety and behavioral despair in rats. Physiology & Behavior. 2009;**97**:420-425

[73] Walf AA, Frye CA. Administration of estrogen receptor beta-specific selective estrogen receptor modulators to the hippocampus decrease anxiety and depressive behavior of ovariectomized rats. Pharmacology Biochemistry and Behavior. 2007;**86**:407-414

[74] Kageyama A, Sakakibara H, Zhou W, Yoshioka M, Ohsumi M, Shimoi K, Yokogoshi H. Genistein regulated serotonergic activity in the hippocampus of ovariectomized rats under forced swimming stress. Bioscience, Biotechnology, and Biochemistry. 2010; **74**:2005-2010

[75] Wang YF, Xu ZK, Yang DH, Yao HY, Ku BS, Ma XQ, Wang CZ, Liu SL, Cai SQ. The antidepressant of secoisolariciresinol, a lignan- type phytoestrogen constitutent of flagseed on ovariectomized mice. Journal of Natural Medicines. 2013;**67**:222-227

[76] Bhandari P. Pomegranate (*Punica granatum L*). Ancient seeds for modern cure? Review of potential therapeutic applications. International Journal of Nutrition, Pharmacology, Neurological Disease. 2012;**2**:171-184

[77] Zhang L, Fu Q, Zhang Y. Composition of anthocyanins in pomegranate flowers and their antioxidant activity. Food Chemistry. 2011;**127**(4):1444-1449. DOI: 10.1016/j. foodchem.2011.01.077

[78] Lipińska L, Klewicka E, Sójka M. Structure, occurrence and biological activity of ellagitannins: A general review. Acta Scientiarum Polonorum, Technologia Alimentaria. 2014;**13**(3):289-299

[79] Al-Muammar MN, Khan F. Obesity: The preventive role of the pomegranate (*Punica granatum*). Nutrition. 2012;**28**(6):595-604

[80] González-Trujano ME, Pellicer F, Mena P, Moreno DA, García-Viguera C. Antinociceptive and anti-inflammatory activities of a pomegranate (*Punica granatum L.*) extract rich in ellagitannins. International Journal of Food Sciences and Nutrition. 2015;**7486**(June 2016):1-5

[81] Yuan T, Ma H, Liu, W, Niesen DB, Shah N, Crews R, Seeram NP. Pomegranate's neuroprotective effects against alzheimer's disease are mediated by urolithins, its Ellagitannin-Gut microbial derived metabolites. ACS Chemical Neuroscience. 2016;**7**:26-33

[82] Naveen S, Siddalingaswamy M, Singsit D, Khanum F. Anti-depressive effect of polyphenols and omega-3 fatty acid from pomegranate peel and flax seed in mice exposed to chronic mild stress. Psychiatric and Clinical Neurosciences. 2013;**67**:501-508

[83] Abdul RS, Abdul KB, Hidayat BMT, Mohd MMA. Antidepressant-like effect of methanolic extract of *Punica granatum* (pomegranate) in mice model of depression. Journal of Natural Products and Biomedical Research. 2015;**1**:16-20

[84] Shastry R, Sharma A, Sayeli V, Sheetal D. Screening of antidepressant activity of *Punica granatum* in mice. Journal Pharmacognosy. 2017;**9**(1):27-29

[85] Díaz MAG. Calidad nutracéutica de extractos de granada dulce y ácida y bioaccesibilidad de sus compuestos fenólicos en un modelo in vivo. PhD Proposal. 2014;**1**

[86] Choi DW, Kim JY, Choi SH, Jung HS, Kim HJ, Cho SY, Chang SY. Identification of steroid hormones in pomegranate (*Punica granatum*) using HPLC and GC–mass spectrometry. Food Chemistry. 2006;**96**:562-571

[87] Middha SK, Usha T, Pande V. HPLC evaluation of phenolic profile, nutritive content, and antioxidant capacity of extracts obtained from *Punica granatum* fruit peel. Advances in Pharmacological Sciences. 2013;**2013**:296236

[88] Van Elswijk D, Schobel UP, Lansky EP, Irth H, Van der Greef J. Rapid dereplication of estrogenic compounds in pomegranate (*Punica granatum*) using on-line biochemical detection coupled to mass spectrometry. Phytochemistry. 2004;**65**:233-241

[89] Espín JC. Biological significance of the gut microbial ellagic acid-derived metabolites urolithins. JournalHindawi. 2013; **2013**: 1-16

[90] Auerbach L, Rakus J, Bauer C, Gerner C, Ullmann, R, Wilmmer H, Huber J. Pomegranate seed oil in women with menopausal symptoms: A prospective randomized, placebo-controlled, double blinded trial. Menopause. 2012;**19**(4):426-432

[91] Shuid AN, Mohamed IN. Pomegranate use to attenuate bone loss in major musculoskeletal diseases: An evidence-based review. Current Drug Targets. 2013;**14**:1565-1578

[92] Mori-Okamoto J, Otawara-Hamamoto Y, Yamato H, Yoshimura H. Pomegranate extract improves a depressive state and bone properties in menopausal syndrome model ovariectomized mice. Journal of Ethnopharmacology. 2004;**92**:93-101

[93] Rodríguez M. Respuestas fisológicas moleculares y fitoquímicas de variedades *de Brassica oleracea* (grupo itálica) sometidas a estrés abiótico [Tesis recepcional de Doctorado]. España: Universidad de Murcia; 2013

[94] Álvarez PE, de la Rosa LA, González-Aguilar GA, Ayala-Zavala JF. Antioxidantes en alimentos y salud. México: Clave Editorial; 2012. pp. 97-289

[95] Klejin MJ, Van Der YT, Wilson PW, Adlerercreutz H, Mazur W, Grobbe DE, Jacques PF. Intake of dietary phytoestrogens is low postmenopausal women in the United States: The Framingham Study (1-4). Journal of Nutrition. 2001;**131**:1826-1832

[96] Nardini MD' Aquino N, Tomassi G, Gentili V, Di Felice M, Scaccini C. Inhibition of human Low-Density lipoprotein oxidation by Caffeic acid and other hydroxycinnamic acid derivatives. Journal Free Radical Biology & Medicine. 1995;**19**(5):541-552

[97] Rodríguez-Amaya D. Estructuras y características de las Xantofilas comunes en los alimentos. En Carotenoides y preparación de alimentos: Retención de los Carotenoides, Provitamina A en los alimentos preparados, procesados y almacenados. Health and Nutrition. 1999; **1**:3-7

[98] Troxler J. Brócoli. Food and Drug Protection. 2001; **303**: 1-35

[99] Fernández-León MF, Fernández León AM, Lozano M, Ayuso MC, González Gómez D. Identificación y cuantificación de glucosinolatos intactos en dos cultivares de brócoli cultivados en las Vegas Bajas del Guadiana (Extremadura). Actas de Horniticultura. 2012;**60**:767-771

[100] Fernández M. Evolución de los parámetros de calidad físico-química y funcional de distintas Brassicas sometidas a diferentes tratamientos postcosecha. Doctorado. Universidad de Extramadura; 2012

[101] Verkerk R, Dekker M, Wim Jongen MF. Post-harvest increase of indolyl glucosinolates in response to chopping and storage of vegetables. Journal of the Science of Food and Agriculture. 2001;**81**:953-958

[102] Shaban H, Richter C. A2E and blue light in the retina: The paradigm of age-related macular degeneration. The Journal of Biological Chemistry. 2002;**383**(3-4):537-545

[103] Martínez A. Carotenoides distribución y estado natural. Doctorado. Universidad de Antioquia; 2003

[104] Vallejo F, Tomás-Barberán F, García-Viguera C. Health-Promoting Compounds in Broccoli as influenced by refrigerated transport and retail sale period. Journal of Agricultural and-FoodChemistry. 2012; **51**: 3029-3034

[105] Young S, Milner JA. Targets for indole-3carbinol in cancer prevention. Journal of Nutritional Biochemistry. 2005;**16**:65-73

[106] Gallardo C, Jiménez L, García-Conesa MT. Hydroxycinnamic acid composition and in vitro antioxidant activity of selected grain fractions. Journal Food Chemistry. 2006; **99**:455-463

[107] Meléndez-Martínez AJ, Vicario IM. Pigmentos carotenoides: Consideraciones estructurales y fisicoquímicas. Archivos Latinoamericanos de Nutrición. 2007;**57**:112-116

[108] Alquézar B. Caracterización bioquímica y molecular de la carotenogénesis en frutos cítricos. Doctorado. Universidad de Valencia; 2007

[109] Ludueña B. Mastandrea C, Chichizola C, Franconi MC. Isoflavonas en soja, contenido de Daidzeína y Genisteína y su importancia biológica. Red de Revistas Cientificas de América Latina, el Caribe, España y Portugal. 2007;**71**:56-66

[110] Begoña A. Efecto de "nuevos" nutrientes sobre la retina y la función visual. Revista de Nutrición Práctica. 2008;**12**:64-69

[111] Bhagwat S, Haytowitz DB, Holden JM. USDA Database for the Isoflavone content of Selected Foods. Vol. 15. Maryland: US Department of Agriculture; 2008. pp. 43-49

[112] Márques A. Mejora genética en glucosinolatos en semillas de mostaza etíope (*Brassica carinata A. Braun*). Doctorado. Universidad de Córdoba; 2008

[113] Mataíx J. Rodríguez-Navarrete J. Tratado de Nutrición y Alimentación. Alimentos funcionales. 4th ed. Barcelona: OCEANO/ ergon (ed); 2009. Chapter 20

[114] Kim DH, Jung HA, Park SJ, kim JM, Lee S, Choi JS, Cheong JH, Ko KH, Ryu JH. The effects of Daidzin and its aglycon, Daidzein, on the Scopolamine induced Memory Impairment in Male Mice. Archives of Pharmacal Research. 2010;**33**(10):1685-1690

[115] Navarro-Cruz AR, Vera-López O, Muñoz-Bedolla M, Melgoza-Palma N, Lazcano-Hernández M, Gómez CrisostomoMR, Romero Vázquez M. Estudio de la concentración de quercetina en las variedades de manzana (*Malus domestica*) Fuji, red delicius y delicia. Red de Revistas Cientificas de América Latina, el Caribe, España y Portugal. 2010;**25**:901-910

[116] Naso L, Lezama L, Rojo T, González Baró AC, Williams-Patricia AM, Ferrer EG. Efectos antioxidantes del ácido clorogénico y su complejo con el catión oxovanadio. Journal Spectroscopy Letters. 2010;**64**:1-7

[117] Aguilera-Ortíz M, Reza-Vargas MC, CHew-Madinaveitia RG, Meza-Velázquez JA. Propiedades funcionales de las antocianinas. Revista de Ciencias Biológicas y de la Salud. 2011;**12**:16-22

[118] Zhang JC, Yao W, Dong C, Yang C, Ren Q1, Ma M, Han M, Wu J, Ushida Y, Suganuma H, Hashimoto K. Prophylactic effects of sulforaphane on depression-like behavior and dendritic changes in mice after inflammation. The Journal of Nutritional Biochemistry. 2017;**39**:134-144

[119] Yao W, Zhang JC, Ishima T, Dong C, Yang C, Ren Q, Ma M, Han M, Wu J, Suganuma H, Ushida Y, Yamamoto M, Hashimoto K. Role of Keap1-Nrf2 signaling in depression and dietary intake of glucoraphanin confers stress resilience in mice. Scientific Reports. 2016;**6**:306-359

[120] Townsend BE, Johnson RW. Sulforaphane reduces lipopolysaccharide-induced proinflammatory markers in hippocampus and liver but does not improve sickness behavior. Nutritional Neuroscience. 2017;**20**:195-202

[121] Townsend BE, Chen YJ, Jeffery EH, Johnson RW. Dietary broccoli mildly improves neuroinflammation in aged mice but does not reduce lipopolysaccharide-induced sickness behavior. Nutrition Research. 2014;**34**:990-999

[122] Fowke JH, Longcope C, Hebert JR. *Brassica* vegetable consumption shifts estrogen metabolism in healthy postmenopausal women. Cancer Epidemiology, Biomarkers & Prevention. 2000;**9**:773-779

[123] Ambrosone CB, McCann SE, Freudenheim JL, Marshall JR, Zhang Y, Shields PG. Breast cancer risk in premenopausal women is inversely associated with consumption of broccoli, a source of isothiocyanates, but is not modified by GST genotype. Journal of Nutrition. 2004;**134**:1134-1138

[124] Mease P. Fibromyalgia syndrome: Review of clinical presentation, pathogenesis, outcome measures, and treatment. The Journal Rheumatology. 2005;**75**:6-21

[125] Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. Arthritis & Rheumatologym. 2001;**44**:222-230

[126] Arnold LM, Hudson JI, Keck PE, Auchenbach MB, Javaras KN, Hess EV. Comorbidity of fibromyalgia and psychiatric disorders. The Journal of Clinical Psychyatry. 2006; **67**:1219-1225

[127] Clauw DJ. Fibromyalgia: A clinical review. The Journal of the American Medical Association. 2014;**311**:1547-1555

[128] Martínez-Jauand M, Sitges C, Femenia J, Cifre I, González S, Chialvo D, Montoya P. Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia. Jounal of Clinical Rheumatology. 2013;**32**:975-981

[129] Kadetoff D, Lampa J, Westman M , Andersson M, Kosek E. Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels. Journal of Neuroimmunology. 2012;**242**:33-38

[130] Prados G, Miro E. Fibromyalgia and sleep: A review. Revista De Neurologia. 2012;**54**: 227-240

[131] Cuatrecasas G, Gonzalez MJ, Alegre C, Sesmilo G, Fernandez-Sola J, Casanueva FF, Garcia-Fructuoso F, Poca-Dias V, Izquierdo JP, Puig-Domingo M. High prevalence of growth hormone deficiency in severe fibromyalgia syndromes. The Journal of Clinical Endocrinology & Metabolism. 2010;**95**:4331-4337

[132] Edwards AM, Blackburn L, Christie S, Townsend S, David J. Food supplement in the treatment of primary fibromyalgia: A double blind, cross over trial of anthocyanidins and placebo. Journal of Nutritional & Environmental Medicine. 2000;**10**:189-199

[133] Griffith MP, Zarrouf FA. A systematic review of chronic fatigue syndrome: Don´t assume it´s depression. Primary Care Companion to the Journal of Clinical Psychiatry. 2008;**10**:120-128

[134] Vasiadi M, Newman J, Theoharides TC. Isoflavones inhibit poly(I:C)-induced serum, brain, and skin inflammatory mediators—relevance to chronic fatigue syndrome. Journal of Neuroinflammation. 2014;**11**:1-12

Chapter 7

The Benefits of Physical Activity on Climacteric Women

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.68829

Abstract

As the population ages, there is a need of developing ways to prevent or revert the deleterious effects of aging, especially in climacteric women who suffer with the problems caused by hormonal changes. Exercise is a nonmedicated intervention that can be applied on that population. The benefits of physical activity can positively change body composition, increase levels of muscular strength, balance, and functional capacity. Strength training, aerobic exercise, whole body vibration, and aquatic exercises are some of the modalities that health professionals can prescript to these individuals. Although there are many studies about these exercises, a technique called blood flow restriction is emerging as an alternative to high load exercises but with the same benefits.

Keywords: climacteric women, exercise, body composition, strength, blood flow restriction

1. Introduction

The aging process, also called senescence, is characterized by gradual and irreversible changes in an organism's structure and operation as a result of the time passing. The World Health Organization (WHO), in the end of the 1990s, adopted the term "active aging" to describe the process of the health, participation, and security opportunities. The aim of the active aging is to increase the expectation and quality of life to all the people who are aging, including the fragile, physically impaired, and the ones that require special care [1]. Data from the WHO indicate that in 2025, the life expectation in the developed countries will be 81 years; and 78 years in the ones that are in the development process [2].

The word "health," according to the WHO, refers to the physical, mental, and social well-being where the organism works optimally without any disease. Therefore, in an active aging project, the politics and programs that promote mental health and social living are just as important as the ones that improve the physical health conditions. Furthermore, the individual will be able to stay physically active and able to work [2].

During the adult life, the physiological functions of our organism decline, which is part of the senescence. The capacity of protein synthesis reduces significantly, there is a decrease of the immunological functions and changes in the body composition. Also, in elderly, the motor performance falls down expressively as a result of physiological degeneration and extrinsic factors such as environment conditions, task requirements, state of the disease, life style, or the combination of these elements. More than just biological and physiological changes, the aging process brings loss of psychological and social character, as well as elderly isolation, with the understanding that they are no longer active, or the fact that they think that are an obstacle to their families what causes sadness, low self-steam, even causing emotional diseases like depression [3].

In the middle-age, about 45 years old, the non-transmissible diseases are responsible for most part of the health complications and deaths. The researches show the risk of chronic diseases as the age advances, such as diabetes, cardiopathy, osteoarthritis, osteoporosis, and sarcopenia. However, what raises the risk of development of chronic diseases at older ages is smoking, sedentarism, inadequate diet, and hormonal alterations [1]. On the other hand, the enrolment in adequate physical activities, healthy diet, nonsmoking, not drinking alcohol, and the right use of the medicaments prescribed by the doctor may prevent diseases and the functional fall, increase the longevity and the individual's quality of life. Regarding specifically the indication of physical activity for the population over 65 years, the American College of Sports Medicine (ACSM) [4] recommends that along with aerobic exercises (moderate or intense), 8–10 strength exercises must be performed, with 8–12 repetitions for each exercise, two time a week.

The reduction of the lean mass close to 50 years is more expressive in women than men. The peak of this reduction happens on the postmenopause period, when occurs the loss of skeletal muscle, which is related to the fall on the production of ovarian hormones (especially, estrogen). The sarcopenia is a syndrome characterized by progressive and generalized reduction of the skeletal muscle mass associated with the loss of muscular strength, having as a consequence the physical impairment (reduction of muscular function and speed), fall in the quality of life and greater mortality. The European Study Group in Sarcopenia on the Elderly recommends that for the sarcopenia diagnostic the individual must have, necessarily, low lean mass associated with one of these two factors: low muscular function or strength. The preservation of the skeletal muscle mass is connected to the well-being and the disease prevention in the elderly [5].

Among the events that happen during the aging process, the reduction on the mineral bone density has a particular important role for the possible development of osteoporosis in both the genders but mostly in the female. After 40 years, the annual bone loss average is from 2 to 3% and elevates to more than 5% in the early years of climacteric [6]. The WHO defines

osteoporosis as the reduction of bone mass associated with the disarrangement of the bone microarchitecture resulting in increased fragility of the bone and an elevated fracture risk [2].

Women in the postmenopause, when submitted to an exercise program based on stretching, balance, strength exercises, and impact exercises associated with hormone therapy (HT), show greater bone mineral density on the femoral neck when compared to the women that only do hormone therapy [7]. The muscle strength reduces fracture risks caused by osteoporosis because it increases the bone mineral content, the strength supported by the noncontractile tissues (tendons and ligaments), improvement in the postural function, and decrease in the risk of fall. Some studies suggest that the growth of muscle mass leads to a rise on the muscular strength, stimulating the bone remodeling through the piezoelectric effect, which is the capacity of the bone to transform mechanic signals into electrical signals [8].

2. Body composition

2.1. Lean and fat mass

The role of physical activity on body and fat mass control is extremely important. Studies demonstrated that there is a negative correlation between regular physical activities and body mass index (BMI). Since the exercise enhances energy expenditure, it plays an important part on reaching the ideal weight and body composition related to the health of elderly people. Therefore, the morbi-mortality, associated with non-transmissible chronic diseases, could be reduced with prevention, including physical activity as a change on the lifestyle to improve the aspects of body composition. Also, a reduction on the muscle mass on climacteric women results in a decrease of the basal metabolic rate, strength, and level of physical activity. However, it is already established that the reduction of these energetic needs is not followed by a decrease on the caloric ingestion, which causes a rise in the body fat mass with aging [9].

The aerobic exercise is a modality that has the power of promoting positive changes in the body composition. However, there is a need of controlling the intensity of the exercise because literature shows that when realized with a very small load, it will not modify the aspects of body composition [10]. A group of postmenopause women performed a 1-hour walking protocol three times a week for 6 months at 60% of the maximum oxygen volume (VO_{2max}) intake, whereas the other group performed walking 5 days a week for the same period but without controlling the intensity. Despite both the groups had shown reduction in fat mass and percentage, only the controlled one had decrease in the body mass.

Still regarding the effects of exercise on body composition, eight postmenopause women and seven men, aged between 61 and 77 years, caucasian, healthy and sedentary, with body mass index (BMI) with normal levels (24.8 kg/m^2) performed a 26-week resistance training protocol to upper and lower limbs and lumbar extensors, three times a week, two series of 10 repetitions for each exercise at 65–80% of one maximum repetition (1RM), totaling 45 min [11]. There were no changes on body mass; however, there was a reduction on fat percent (3.4%) and fat mass (3.1 kg) and an increase of the free-fat mass (2.0 kg), strength (14.9–49.0 kg), total energy expenditure, and basal metabolic rate.

Another aspect that can interfere on the results of exercise on the body composition is the presence or absence of a certified supervisor for the physical activity. Recently, the effects of an exercise program composed of stretching, weight bearing, resistance training for upper and lower limbs, and leisure activities in postmenopause women were evaluated where one group had the supervision of a physiotherapist and the other did not have; the exercises were performed at home. The upper and lower limbs and total body lean mass of the supervised group was increased. On the other hand, that did not happen on the other group, showing that supervision is important to obtain the desired results and also to prevent injuries [12].

The effects of a 16-week variable load resistance exercise protocol on body composition, associated with diet or not, were evaluated in 15 postmenopause women (50–69 years) who performed strength training three times a week with a load of 90% of 1RM [13]. The sample was divided according to the BMI: G1 ($n = 7$; IMC > 27 kg/m^2) and G2 ($n = 8$; IMC < 27 kg/m^2). Group 1 was submitted to the exercise protocol plus diet, whereas the other group did not have the diet controlled. The exercise-only group did not show significant changes on body composition. In comparison, the on-the-exercise + diet group showed a reduction on weight, fat mass, and fat percentage. In that perspective, although the exercise can promote a lot of benefits to climacteric women, if other aspects such as the diet are not well controlled, these benefits may not appear.

2.2. Bone mass

Positive effects of the exercise on the increase or maintenance of bone mineral density (BMD) were already observed in post menopause women with osteopenia or osteoporosis. However, the benefits depend on the type of exercise, intensity, frequency, and duration of the session [14].

Strength training can increase the mechanical stress on bone throughout the tendon promoting an osteogenic response and the piezoelectric effect, justifying the maintenance or increase of BMD. Because of that mechanism, forces of compression, tension, or torsion can generate electric signals that stimulate bone activity and deposition of minerals in stress points caused by muscle contraction. The muscle contraction can increase the BMD and, possibly, block the bone reabsorption [8, 15].

A positive linear relation between BMD and the increase of load during 1 year of strength training in postmenopause women was observed [16]. Exercise programs from low to moderate impact (running, walking, steps up-and-down) are more effective for the preservation of BMD on the lumbar area and femoral neck when combined with strength training than high-impact exercises such as jumping [17].

Many meta-analyses point out that high-intensity aerobic and resistance exercises tend to be more effective for the increase of lumbar spine BMD than low-intensity walking. Nevertheless, when there is an association between low-intensity walking and a high-calcium diet is also effective on elevating BMD. Furthermore, these exercises can promote a 2% elevation on the BMD of postmenopause women, which is a very important improvement in their bone health [18, 19].

Moderate aerobic exercise (50% of the maximum VO_2) seems to be safe and easy to execute in osteoporotic women and effectively increase BMD of the lumbar spine after 12 months of intervention [20]. A well-regulated bone metabolism is extremely important for the prevention and maintenance of the bone system properties. Likewise, a training program can help on the reduction of reabsorption bone biomarkers, reducing the risk of vertebral fracture up to 25%, even if the BMD does not increase significantly [21].

Besides the discrete effect of walking on the lumbar vertebrae BMD, there are other benefits related to that exercise. A 4-hour walking per week showed to be associated to a 41% less hip fracture risk compared to less than 1-hour per week [22]. In the same perspective, 40-minute brisk walking, three times a week, promoted a clinical improvement on the femoral neck BMD and a 35% reduction on the risk of fall on the elderly after 2 years of exercise [23]. **Table 1** sums up a few studies that investigated the benefits of exercise on body composition of climacteric women.

Year	Sample			Exercise protocol	Main results
	n	Age (years)	Stage		
1995 [10]	15	50–69	Postmenopause women	G1: strength training + diet G2: strength training 16 weeks	G1: ↓weight, ↓Percentage fat mass, ↓fat mass, ↑lean mass
1996 [11]	36	X	Postmenopause women	G1: walking, three times a week G2: walking five times a week 24 weeks	G1: ↓Weight, ↓fat mass, ↓ Percentage fat mass G2: ↓Fat mass, ↓ Percentage fat mass
2000 [24]	Eight men and seven women	61–77	Postmenopause	65–80% 1RM strength training, three times a week, 45 minutes' session 26 weeks	↓3, 4% fat mass, ↓fat mass, ↑lean mass
2016 [13]	34	60–74	Postmenopause women	G1: stretching, walking or step, upper and lower limbs strength training, leisure activities, all with supervision G2: same protocol, but without supervision Two times a week 12 months	G1: ↑arms, legs and total lean mass
1997 [23]	97	59–75	Postmenopause women with upper limb fractures	G1: walking, 40 min, three times/week G2: upper limb exercises, guided to perform exercises that improve wrists and arms function, visited each 3 month. Reassessed after 1 and 2 years.	G1: a tendency on the increase of the BMD of the femoral neck; increase on the lumbar BMD in both groups, however not statistically significant

Year	Sample			Exercise protocol	Main results
	n	Age (years)	Stage		
2001 [14]	35	53–77	Osteoporotic postmenopause women	G1: daily walking + 2 series of 15 repetitions per day of exercises for trunk and lower limb muscles and ingestion of calcium and D vitamin G2: detraining group G3: control group	No difference on the BMD of the lumbar vertebral in none of the groups; ↑ Percentage average BMD of the G1 when comparing the baseline to the 1st and 2nd year of training
2003 [7]	140	X	Osteoporotic postmenopause women	G1: hormone therapy + strength training G2: hormone therapy only	There was a positive association between the amount of weight lifted and the BMD of the femur independent from factors such as age, weight, and hormone therapy
2004 [20]	50	X	Osteoporotic postmenopause women	G1: outside walking (50% VO_{2max}, 1 h per day, 4 days a week, for 12 months G2: control group	There was no significant difference on the BMD of both groups The bone marker NTX showed a reduction on the G1

Table 1. Studies related to exercise and body composition in climacteric women.

3. Neuromuscular variables

As an important consequence caused by the many endocrine, neuroendocrine, behavioral, and metabolic changes that occur on the climacteric period, the decline of neuromuscular variables is one of the most frequent that brings important alterations to the life of this population [24]. During this chapter, the term "neuromuscular variables" will be used to make reference to all capacities that are related to neural stimulus and muscle health such as strength, agility, speed, flexibility, balance, and others.

There is a direct relation between muscle mass loss and strength decrease in women with more than 40 years. It is estimated that the muscle strength has a 15% fall on the period between 60 and 79 years, and 30% from the eighth life decade, with the lower limbs being more affected than the upper limbs [25, 26].

The diminution of muscle strength as a result of changes in the composition of the subtypes of muscle fiber, oxidative stress, variations of the growing hormone (GH), IGF-1, insulin, among others, also leads to a reduction in other important physical capacities that depends on the strength [27]. Body balance, walking speed, stepping up-and-down, recovery after a stability loss and standing up from the chair are some examples of variables that, with the fall in strength, end up being negatively affected.

The Brazilian Society of Sports Medicine [28] published an official statement regarding physical activity and women's health pointing that there is an inverse relation between exercising

regularly and the main causes of death in menopause women. Thus, performing physical exercises regularly is the most effective way of avoiding strength loss, or try to regain part of the strength that was lost, similarly all the other capacities that depends on strength [26].

There are many types of exercise that promote benefits for the neuromuscular variables of climacteric women. Strength training, in general, is the most well-studied and used to achieve that goal. To prescribe correctly the most adequate training, few factors are to be taken into consideration such as the number of repetitions, load, series, resting interval, seminal frequency and others. The American College of Sports Medicine [4] states that to have effective results with the strength training, the load should be bigger than 65% of one maximum repetition (1RM), three series with 8–12 repetitions for the main muscle groups of the upper and lower limbs should be performed, at least three times a week. Nonetheless, those training variables can be manipulated in many ways, allowing the creation of a lot of training programs.

It is also well-known that training with higher intensities promote bigger changes. When comparing a training protocol that followed all the statements of the ACSM, which means exercises that involved the main muscle groups from upper and lower body where one group trained at 40% and the other at 80% of 1RM, it was observed that despite the fact that both showed increase of strength and transverse muscle section, the high intensity group had significantly more gains. In addition, it is important to highlight that in this specific study, emphasis was given to exercises that activated muscles that had origin or insertion on the spine and femur aiming to ally the strength gain with the piezoelectric effect and, consequently, improve the bone mass, which can be an interesting way to potentialize the benefit of the resistance exercise [29].

Although muscle strength happens to be a variable relatively easy to increase or, at least, maintain, it must be highlighted that if the individual stops practicing the physical activity, the detraining also happens fast. To illustrate that 15 postmenopause women practiced strength exercises for upper and lower limbs for 8 weeks with a load of 80% of 1RM and that was effective to increase strength of the trained muscle groups. To analyze the detraining process, those women stopped training and re-evaluated after 8 weeks. The average of strength loss was 4.5% after detraining. Yet, it is important to say that there was no difference between the strength before the training and after detraining [30]. Hence, the strength training is effective to climacteric women, but its benefits are easily lost in cases of abandoning the exercise program, pointing out the importance of developing strategies that increase the adherence of these women to the training.

A group of researchers from the Idaho State University, United States, developed a training program called POWIR (Prevent Osteoporosis with Impact + Resistance) with the initial goal of bone improvement but was modified to improve strength and function also. The basis of this program is composed of a progressive training that uses dumbbells, barbells, and weighted vests as ways of applying resistance focusing on exercises for the lower limbs, hips, chest, and back [31]. This protocol was initially created to healthy climacteric women; however, it was also applied in postmenopause women who had breast cancer.

In this specific population, 106 women who went through breast cancer treatment were separated in two groups where one performed the POWIR protocol and the other an exercise program consisted only of stretching and flexibility, called FLEX. The intervention lasted for 1 year and in addition to the exercises already pointed, both groups performed home exercises

one time per week. The POWIR was able to improve aspects such as muscle strength, walking speed, stand up from the chair, among others, showing to be an efficient and safe option for climacteric women, including the ones who had diseases like cancer [31].

Water exercises are another type of physical activity that can improve neuromuscular variables of climacteric women and the changes may be similar to other exercises that are commonly used on the daily practice of physiotherapists and personal trainers, such as elastic bands. A water exercises protocol with the same number of repetitions, rest interval, series, week frequency, duration (35–60 min) and for the same muscle groups of an elastic band protocol promote the similar benefits for climacteric women [32].

Nevertheless, even with the same exercises, some differences still appear when comparing water exercises and elastic bands. The water exercises were more efficient on improving the performance on the 60-second squats (65%) and abdominal crunch (28%), whereas the elastic bands were better to increase flexibility (44.19%) and performance on the knee push-up (29.13%). Still, it is important to highlight that both protocols promoted benefits in all neuromuscular variables [32]. When the protocol is well designed with heating, stretching, strength exercises, and cool down, there is no doubt that the benefits will appear, and both water exercises and strength training with elastic bands are effective to climacteric women.

In fact, to promote a muscle strength gain, it is necessary that the muscle contracts and so activate mechanisms that promote protein synthesis. In more intense exercises such as strength training or water exercises, it is very easy to observe how the contraction needed to win a load stimulates muscle hypertrophy and strength gains. On the other hand, lighter activities such as whole body vibration training (WBVT) sessions also stimulate muscle contraction [33]. The most important mechanism activated is that the vibration has the capacity of stimulating sensorial receptors that lead to a reflect activation of the motor units, similar to what happens on the tonic reflex [34].

Hormone therapy (HT) on climacteric women is an important treatment indicated to reduce the symptoms (such as, heat waves, night sweats, vaginal dryness, changes in sleep, among others) caused by decrease of hormones, mainly estrogen [35, 36]. Studies confirmed the positive effects of this therapy on the quality of life and strength in postmenopausal women [37, 38]. Associated with HT, physical exercise can bring benefits to women's health after menopause, reduce fat mass and the risk of coronary diseases; increase strength, resistance, and flexibility [39–41]. Besides that, weight-bearing, strength, and balance exercises associated with HT are able to help in osteoporosis prevention and treatment in a 1-year period, aiming to increase BMD and, consequently, reducing the number of lumbar and femur neck fractures [16].

It is undeniable that the strength training is the type of exercise mostly used to promote strength gains. In this perspective, to see if the WBVT is also capable of promoting those gains, the results of both types of exercise must be compared. Three times a week WBVT and strength training, for 6 months, were able to increase significantly the isometric (15.10% and 16.49%, respectively) and isotonic (16.47% and 10.59%) strength, those differences being nonsignificant when comparing both types of training [34]. Thus, WBVT can promote a strength increase similar to the strength training. Some studies that analyzed the effects of many types of exercise on the neuromuscular variables are listed on **Table 2**.

Year	Sample			Exercise protocol	Main results
	n	Age (years)	Stage		
2000 [29]	25	41–60	Postmenopause women	G1: strength training at 80% of 1RM G2: strength training at 40% of 1RM G3: control group	G1 and G2: ↑muscle strength, ↑transverse muscle section G1: showed significant greater increases
2002 [30]	15	49–62	Postmenopause women	G1: strength training at 80% of 1RM G2: control group	G1: increased strength after 8 weeks, but that improvement was lost after 8 weeks of detraining
2012 [31]	106	≥50	Postmenopause women survivors of breast cancer G2: FLEX Both interventions lasted 1 year	G1: POWIR	G1: ↑ muscle strength, ↑walking speed, ↑stand up from the chair
2009 [32]	46	54.7 ± 2.0	Postmenopause women	G1: water exercises G2: strength training with elastic bands	Both groups: ↑60-second squats, ↑abdominal crunch, ↑flexibility, ↑knee push-up
2004 [34]	70	58–74	Postmenopause women	G1: whole body vibration (24 weeks) G2: strength training (24 weeks) G3: control group	G1 and G2: ↑isometric and isotonic strength

Table 2. Studies related to exercise and neuromuscular variables in climacteric women.

4. Blood flow restriction—an alternative to high loads

As previously said, to obtain maximum benefits from exercise, for example the strength training, it is indicated that higher loads must be used, which will promote a bigger response of the organism and, consequently, greater benefits [42]. Nevertheless, loads bigger than 65% of 1RM as stated by the ACSM [4] many times are not tolerated by the elderly, individuals with some disease that turns harder performing exercises, such as chronic obstructive pulmonary disease and osteoporosis, among other populations. In this perspective, a Japanese scientist called Yoshaki Sato thought about a method that consisted of low-load exercises associated with some device that could reduce the blood flow, for example pneumatic cuffs, elastic bands, and sphygmomanometers (**Figure 1**), to the muscle that is being used [43]. Initially, the method was called "vascular occlusion", but nowadays, the terms "Kaatsu training" and "blood flow restriction" (BFR) are the most widely used.

There are still many unanswered questions regarding how the BFR is capable of promoting benefits on strength, functionality, muscle activation, and others, similar to the traditional high

Figure 1. (A) Walking with blood flow restriction, (B) strength training with blood flow restriction, and (C) pneumatic cuff used to promote the blood flow restriction.

load exercise, even being performed with very low loads. However, studies that investigated the BFR mechanisms affirm that the explanation lies on a bigger metabolite concentration, stimulation of anaerobic growth factors, greater fast twitch fibers recruitment, increase on GH secretion, VGF1, fall on miostatine and rise on mTOR levels, greater nitric oxide synthesis, along with other factors that were not yet discovered [44–46].

Most part of the studies with BFR combine this technique with the strength training and in apparently healthy individuals; however, some researchers already have been investigating how the BFR can be used in special populations and associated with other types of exercise [47–52]. In the next session, some studies that used this technique in climacteric women and/or with non-transmissible chronic diseases will be presented.

4.1. Applying the blood flow restriction

The osteoporosis, which is a bone-metabolic disorder characterized by a reduction of the bone mineral density (BMD) with deterioration of the bone micro architecture, leading to an increase of the bone fragility and fracture risk [53], affects climacteric women, and this is a population that needs to practice exercises to improve not only the bone, but also the neuromuscular aspects. Because of that, strength training with blood flow restriction is being used in osteoporotic women due to the fact that it can promote benefits without the need of elevated loads [47].

A low load (30% of 1RM) with BFR and a high load (80% of 1RM) strength training program were applied for 3 months and two times a week in women with osteoporosis (62.60 ± 4.33 years) to compare the alterations on strength levels [47]. Both protocols consisted of four series until concentric failure, but while the BFR group had a 30 seconds' rest between series, the high load group had 2 minutes. The two types of exercises were capable of increasing strength comparing the pre-test in the 6 and 12 weeks, and the gains were similar for both groups, showing that even with low load, the BFR promotes strength gains on the same magnitude of high loads.

There is few literature regarding the use of BFR in water exercises probably because of the problems that can appear on building a restriction equipment that could be easily used on water. Even with those difficulties, two studies were developed by a group of researchers from the Federal University of Paraíba, Brazil, associating water exercises for BFR [48, 49]. Menopaused women (n = 28) were separated in control group, water exercises and water exercises with BFR. For 8 weeks, the experimental groups performed a 45 minutes' exercise protocol for lower limbs in a pool with controlled temperature, being on with and without BFR. The exercise combined with BFR increased lower limbs maximum strength, which did not happen on the other experimental group. Also, both groups improved functional performance [48]. In contrast, neither of the protocols were capable of changing aspects of the body composition, probably because the exercise volume was too low to promote such changes [49].

Elastic band exercises are another type of exercise whose effects associated with BFR were investigated. Similar to the traditional strength training, low-load elastic band exercises with BFR for upper limbs for 2 months, three times a week, showed an increase on the strength similar to the high intensity group. In addition, a tendency for improving the total bone mass was also found [50].

Even though the mechanisms of BFR on the improvement of the muscle health are not completely well known, some studies were already able to partially explain that [44, 45]. Regarding the bone mass, few are the studies explaining the physiological mechanisms caused by BFR. However, since it is a low-load exercise, the improvements do not come from mechanical stimulus or piezoelectric effect but from metabolic and hormonal factors [51, 52]. The low-load strength training with BFR was capable of increasing the bone alkaline phosphatase levels in elderly men after 6 weeks of exercise, correspondingly to the high load group (21% and 23%, respectively) [51]. Besides that, there is the hypothesis that an increase on the intramedullary pressure and interstitial fluid flow within the bone promoted by the BFR leads to favorable responses for bone formation and remodulation [52].

5. Conclusions

With the aging of the world's population, it turns even more necessary that new studies be developed with the goal of finding exercise types that benefits this population group, aiming not only the treatment of non-transmissible chronic disease but also its prevention. The positive effects of exercise in climacteric women were already proved in a lot of studies, and it is essential that the health professionals responsible for the prescription of such exercises (physiotherapists, personal trainers, occupational therapists) have the necessary knowledge to prescribe correctly in a way that brings maximum improvements on body composition, functional performance, strength, balance, and others. On the other hand, new ways of exercise, just like blood flow restriction, are promissory exercise modalities for that the public still needs more studies regarding the ideal prescription to apply this technique on climacteric women.

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References

[1] World Health Organization (WHO). Active Aging: A Health Politics. Brasilia; 2005

[2] World Health Organization (WHO). Global Forum for Health Research: The 10/90 Report on Health Research. Genebra; 2000

[3] Mazo GA, Lopes MA, Bertoldo BT. Atividade física e o idoso: concepção gerontológica. 2nd ed. São Paulo: Sulina; 2004. p. 236

[4] American College of Sports Medicine (ACSM). Position stand: Progression models in resistance training for healthy adults. Medicine and Science in Sports and Exercise. 2009;**3**:687-708

[5] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010;**39**:412-423

[6] Silverman SL, Piziak VK, Chen P, Misurski DA, Wagman RB. Relationship of health related quality of life to prevalent and new or worsening back pain in postmenopausal women with osteoporosis. Journal of Rheumatology. 2005;**32**:2405-2409

[7] Teixeira PJ, Going SB, Houtkooper LB, Metcalfe LL, Blew RM, Flint-Wagner HG, et al. Resistance training in postmenopausal women with and without hormone therapy. Medicine and Science in Sports and Exercise. 2003;**35**:555-562

[8] Fukada E, Yasuda I. On the piezoelectric effect of bone. Journal of the Physical Society of Japan. 1957;**12**:1158-1162

[9] Melby C, Commerford S, Hill J. Perspectives in exercise science and sports medicine vol. 11: Exercise, nutrition, and weight control. In: Lamb D, Murray R, editors. Exercise, Macronutrient Balance, and Weight Control. Carmel: Cooper Publishing Group; 1998. pp. 1-60

[10] Ready AE, Naimark B, Ducas J, Sawatzky J-AV, Boreskie SL, Drinkwater DT, et al. Influence of walking volume on health benefits in women post-menopause. Medicine and Science in Sports and Exercise. 1996;**28**:1097-105

[11] Hunter GR, Wetzstein CJ, Fields DA, Brown A, Bamman MM. Resistance training increases total energy expenditure and free-living physical activity in older adults. Journal of Applied Physiology. 2000;**89**:977-984

[12] Bittar ST, Maeda SS, Marone MMS, Santili C. Physical exercises with free weights and elastic bands can improve body composition parameters in postmenopausal women: WEB protocol with a randomized controlled trial. Menopause. 2016;**23**:383-389

[13] Ryan AS, Pratley RE, Elahi D, Goldberg AP. Resistive training increases fat-free mass and maintains RMR despite weight loss in postmenopausal women. Journal of Applied Physiology. 1995;**79**:818-823

[14] Iwamoto J, Takeda T, Ichimura S. Effect of exercise training and detraining on bone mineral density in postmenopausal women with osteoporosis. Journal of Orthopaedic Science. 2001;**6**:128-132

[15] Bonewald LF, Johnson ML. Osteocytes, mechanosensing and Wnt signaling. Bone. 2017;**42**:606-615

[16] Cussler EC, Lohman TG, Going SB, Houtkooper LB, Metcalfe LL, Flint-Wagner HG, et al. Weight lifted in strength training predicts bone change in postmenopausal women. Medicine and Science in Sports and Exercise. 2003;**35**:10-17

[17] Martyn-St James M, Carroll S. A meta-analysis of impact exercise on postmenopausal bone loss: The case for mixed loading exercise programmes. British Journal of Sports Medicine. 2009;**43**:898-908

[18] Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. Journal of Bone and Mineral Research. 1996;**11**:1539-1544

[19] Kelley GA, Kelley KS, Tran ZV. Exercise and lumbar spine bone mineral density in postmenopausal women: A meta-analysis of individual patient data. Medical Sciences. 2002;**57**:599-604

[20] Yamazaki S, Ichimura S, Iwamoto J, Takeda T, Toyama Y. Effect of walking exercise on bone metabolism in postmenopausal women with osteopenia/osteoporosis. Journal of Bone and Mineral Metabolism. 2004;**22**:500-508

[21] Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. American Journal of Medicine. 2017;**112**:281-289

[22] Feskanich D, Willett W, Colditz G. Walking and leisure-time activity and risk of hip fracture in postmenopausal women. Journal of the American Medical Association. 2002;**288**:2300-2306

[23] Ebrahim S, Thompson PW, Baskaran V, Evans K. Randomized placebo-controlled trial of brisk walking in the prevention of postmenopausal osteoporosis. Age Ageing. 1997;**26**:253-260

[24] De Villiers TJ, Gass MLS, Haines CJ, Hall JE, Lobo RA, Pierroz DD, et al. Global Consensus Statement on menopausal hormone therapy. Climacteric. 2013;**16**:203-204

[25] Orsatti FL, Dalanesi RC, Maestá N, Náhas EAP, Burini RC. Redução da força muscular está relacionada à perda muscular em mulheres acima de 40 anos. Rev Bras Cineantropometria e Desempenho Hum. 2011;**13**:36-42

[26] Macaluso A, De Vito G. Muscle strength, power and adaptations to resistance training in older people. European Journal of Applied Physiology. 2004;**91**:450-472

[27] Maltais ML, Desroches J, Dionne IJ. Changes in muscle mass and strength after menopause. Journal of Musculoskeletal and Neuronal Interactions. 2009;**9**:186-197

[28] Leitão M, Lazzoli J, Oliveira M, Nóbrega A, Silveira G, Carvalho T, et al. Posicionamento oficial da Sociedade Brasileira de Medicina do Esporte: Atividade física e saúde na mulher. Revista Brasileira de Medicina do Esporte. 2000;**6**:215-220

[29] Bemben DA, Fetters NL, Bemben MG, Nabavi N, Koh ET. Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. Medicine and Science in Sports and Exercise. 2000;**32**:1949-1957

[30] Elliott KJ, Sale C, Cable NT. Effects of resistance training and detraining on muscle strength and blood lipid profiles in postmenopausal women. British Journal of Sports Medicine. 2002;**36**:340-344

[31] Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: A randomized controlled trial. Journal of Cancer Survivorship. 2012;**6**:189-199

[32] Colado JC, Triplett NT, Tella V, Saucedo P, Abellán J. Effects of aquatic resistance training on health and fitness in postmenopausal women. European Journal of Applied Physiology. 2009;**106**:113-122

[33] Moreira L, Oliveira M, Galvão A, Marin-Mio R, Santos R, Castro M. Physical exercise and osteoporosis: Effects of different types of exercises on bone and physical function of postmenopausal women. Arquivos Brasileiros de Endocrinologia & Metabologia. 2014;**58**:514-522

[34] Verschueren SMP, Roelants M, Delecluse C, Swinnen S, Vanderschueren D, Boonen S. Effect of 6-month whole body vibration training on hip density, muscle strength, and postural control in postmenopausal women: A randomized controlled pilot study. Journal of Bone and Mineral Research. 2004;**19**:352-359

[35] Rebar R, Trabal J, Mortola J. Low-dose esterified estrogens (0.3 mg/day): Long term and short-effects on menopausal symptoms and quality of life in postmenopausal women. Climacteric. 2000;**3**:176-182

[36] Dennerstein L, Lehert P, Guthrie J, Burger H. Modeling women's health during the menopausal transition: A longitudinal analysis. Menopause. 2007;**14**:53-62

[37] Genazzani A, Niccolucci A, Campagnoli P, Crosigani P, Nappi C, Serra G. Assessment of the QoL in Italian menopausal women: Comparison between HRT users and non users. Maturitas. 2002;**42**:267-280

[38] Skelton D, Philips S, Bruce S, Naylor C, Woledge R. Hormone replacement therapy increases isometric muscle strength of adductor pollicis in postmenopausal women. Clinical Science (London). 1999;**4**:357-364

[39] Reubinoff B, Wurtman J, Rojansky N, Adler D, Stein P, Schenker J, et al. Effects of hormone replacement therapy on weight, body composition, fat distribution, and food intake in early postmenopausal women: A prospective study. Fertility and Sterility. 1995;**64**:963-968

[40] Schmitz K, Jacobs DJ, Leon A, Schreiner P, Sternfeld B. Physical activity and body weight: Associations over ten years in the CARDIA study. Coronary Artery Risk Development in Young Adult. International Journal of Obesity and Related Metabolic Disorders. 2000;**24**:1475-1487

[41] Teoman N, Ozcan A, Acar B. The effect of exercise on physical fitness and quality of life in postmenopausal women. Maturitas. 2004;**47**:71-77

[42] Laurentino G, Ugrinowitsch C, Aihara AY, Fernandes AR, Parcell AC, Ricard M, et al. Effects of strength training and vascular occlusion. International Journal of Sports Medicine. 2008;**29**:664-667

[43] Sato Y. The history and future of KAATSU Training. International Journal of KAATSU Training and Research. 2005;**1**:1-5

[44] Kawada S. What phenomena do occur in blood flow-restricted muscle? International Journal of KAATSU Training and Research. 2005;**1**:37-44

[45] Loenneke JP, Wilson GJ, Wilson JM. A mechanistic approach to blood flow occlusion. International Journal of Sports Medicine. 2010;**31**:1-4

[46] Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. Sport Medicine. 2015;**45**:187-200

[47] Silva J, Neto G, Freitas E, Pereira Neto E, Batista G, Torres M, et al. Chronic effect of strength training with blood flow restriction on muscular strength among women with osteoporosis. Journal of Exercise Physiology. 2015;**18**:33-41

[48] Araújo JP, Neto GR, Loenneke JP, Bemben MG, Laurentino GC, Batista G, et al. The effects of water-based exercise in combination with blood flow restriction on strength and functional capacity in post-menopausal women. Age (Omaha). 2015;**37**:110-118. DOI 10.1007/s11357-015-9851-4

[49] Araújo J, Rodrigues Neto G, Silva J, Silva H, Pereira Neto E, Batista G, et al. Does water aerobics with blood flow restriction change the body composition? Journal of Exercise Physiology. 2015;**18**:25-31

[50] Thiebaud RS, Loenneke JP, Fahs CA, Rossow LM, Kim D, Abe T, et al. The effects of elastic band resistance training combined with blood flow restriction on strength, total bone-free lean body mass and muscle thickness in postmenopausal women. Clinical Physiology and Functional Imaging. 2013;**33**:344-352

[51] Karabulut M, Bemben DA, Sherk VD, Anderson MA, Abe T, Bemben MG. Effects of high-intensity resistance training and low-intensity resistance training with vascular restriction on bone markers in older men. European Journal of Applied Physiology. 2011;**111**:1659-1667

[52] Loenneke JP, Young KC, Fahs CA, Rossow LM, Bemben DA, Bemben MG. Blood flow restriction: Rationale for improving bone. Medical Hypotheses. 2012;**78**:523-527

[53] Pinto Neto AM, Soares A, Urbanetz AA, Souza ACDAE, Ferrari AEM, Amaral B, et al. Brazilian consensus on osteoporosis 2002. Revista Brasileira De Reumatologia. 2002;**42**:343-354

Edited by Juan Francisco Rodriguez-Landa and Jonathan Cueto-Escobedo

Menopause is a natural state of development in women, but it is also a period of vulnerability to the development of several disorders, such as vasomotor symptoms, hot flashes, vaginal dryness, osteoporosis, cognitive deterioration, depression, and anxiety. Factors as diverse as culture, diet, exercise, maternity, age, and genetics can influence the severity of symptoms that are experienced during menopause and can modify the response to diverse therapies. Studying menopause from a multidisciplinary perspective will help elucidate the different factors that affect health during this specific stage of a woman's life. This book presents several aspects of menopause, including its evolutionary origins, novel nonhormonal therapies, and the neurobiology of related disorders.

ISBN 978-953-51-4708-4

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