



Unmasking the Hidden Links: Menopause, Andropause, and the Metabolic Puzzle. A Narrative Review

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Abstract

Aging is an inherent aspect of human life and is characterized by a plethora of physiological changes that occur within the body. One notable manifestation of aging is the onset of menopause in women and andropause in men, resulting in significant hormonal imbalances. During these transitional phases, the maintenance of optimal health and prevention of chronic diseases and metabolic imbalances are of utmost importance. Consequently, nutritional and dietary interventions have emerged as pivotal factors substantial in promoting healthy aging and mitigating the risk of these conditions. The aim of this literature review was to comprehensively explore the current understanding of the role of hormonal imbalances in metabolic disorders, with a specific emphasis on menopause and andropause. These life stages are known for their hormonal fluctuations that can have a significant impact on metabolic health. Nutritional and dietary interventions have gained attention as potential adjunctive treatments for imbalanced hormones and their associated metabolic consequences. By examining the available evidence, this review seeks to identify and evaluate the effectiveness of specific interventions and provide evidence-based recommendations for health-care professionals and individuals seeking alternative approaches to optimize metabolic health during menopause and andropause.

Keywords: Andropause, hormones, menopause, metabolic health.

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Hormonal imbalances during menopause and andropause have been recognized as influential factors in the development and progression of metabolic health problems. Menopause and andropause are natural life stages characterized by significant hormonal fluctuations, including declines in reproductive hormones such as estrogen, progesterone, testosterone, and follicle-stimulating hormone (FSH). These changes can substantially impact metabolic health, which encompasses conditions such as obesity, type 2 diabetes, cardiovascular diseases, dyslipidemia, and even cancers. Investigating the role of hormonal imbalances in menopause and andropause on metabolic health is of paramount

importance given the prevalence and impact of metabolic disorders on individuals' overall well-being and quality of life. By conducting a comprehensive literature review, this study aimed to synthesize existing research and provide an inclusive understanding of the relationship between hormonal imbalances during menopause and andropause and metabolic health outcomes for developing effective therapeutic strategies.

Menopause is a multifaceted process consisting of various phases, each playing a crucial role in understanding the physiological and hormonal changes that occur during this transformative period in a woman's life.^[1] The initial phase, termed pre-menopause, occurs when a woman experiences

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regular menstrual cycles and is in her prime reproductive years, typically without noticeable menopausal symptoms. Following pre-menopause is the transitional phase known as perimenopause, which spans 2–8 years of significant hormonal fluctuations. During this period, women may encounter irregular menstrual cycles, hot flashes, mood changes, sleep disturbances, or metabolic imbalances.^[2]

Menopause itself marks the conclusion of the reproductive phase in a woman's life, signified by the permanent cessation of menstruation due to the loss of ovarian follicular function. This physiological event is diagnosed retrospectively after a continuous absence of menstruation for 12 consecutive months, with the average age of occurrence being 51 years. Post-menopause follows menopause, commencing 1 year after the last menstrual cycle. This phase can extend throughout the remainder of a woman's life and may include persistent symptoms experienced during perimenopause, such as hot flashes, night sweats, mood changes, sleep disturbances, and urinary issues.^[2]

It is important to note that every woman's experience with menopause is unique, with varying symptoms, durations, and intensities influenced by genetic factors, medical conditions, and lifestyle choices. Additional factors leading to menopause include premature ovarian failure, surgery-induced menopause from hysterectomy, and certain chemotherapy or radiation treatments.^[3]

Human females and selected whale species experience a significant post-reproductive period, where they no longer engage in reproduction. Older females may take on mentorship roles, guiding younger counterparts.^[4] This distinguishes women from other species, as men can father children into their nineties despite a decline in reproductive function.^[4]

Andropause, also referred to as late-onset hypogonadism or male menopause, is characterized by a gradual decline in testosterone levels in men. Unlike menopause, andropause has a more subtle onset and progresses slowly, commonly observed in older men with symptoms such as reduced sexual desire, erectile dysfunction, and morning erection.^[5] The diagnosis involves assessing symptoms suggestive of testosterone deficiency and confirming low testosterone levels. Testosterone replacement therapy can alleviate symptoms and enhance the quality of life for men experiencing andropause, but potential risks must also be considered, including impacts on conditions such as prostate and breast cancers, cardiovascular health, and blood clot formation.^[6]

Male hypogonadism includes two primary types: primary and secondary hypogonadism.^[7] Primary hypogonadism,

or primary testicular failure, is characterized by impaired testicular function despite overstimulation of the hypothalamus and pituitary gland. This may arise from genetic disorders, autoimmune diseases, infections, hemochromatosis, and radiation exposure. Secondary hypogonadism occurs due to dysfunction of the hypothalamus or pituitary gland, affecting testosterone production, and can be caused by obesity, aging, tumors, trauma, infections, medications, and genetic disorders such as Kallmann's syndrome.^[7,8]

It is crucial to mention that andropause is not a natural part of aging, and its symptoms may overlap with other conditions. An accurate diagnosis and comprehensive evaluation are essential. Before pursuing testosterone therapy, exploring dietary and lifestyle modifications can be beneficial.

Moreover, environmental toxins and endocrine disruptors—commonly found in food, water, and consumer products—are linked to metabolic syndrome (MetS) and reduced testosterone levels in males. These substances interfere with normal endocrine function; for example, xenoestrogens mimic estrogen, disrupt testosterone production, and negatively impact reproductive health.^[9]

This literature review recapitulates the existing knowledge on hormonal imbalances during menopause and andropause and their impact on metabolic health. It explores the connection between reproductive hormonal fluctuations and metabolic outcomes, highlighting potential therapeutic nutritional and dietary interventions for managing hormonal imbalances and mitigating metabolic derangements.

Hormonal Imbalances in Metabolic Disorders

Metabolic disorders, or MetS, comprise interconnected conditions that elevate the risk of cardiovascular disease, type 2 diabetes, and other health issues. They are characterized by abdominal adiposity, hypertension, hyperglycemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol levels.^[10] The prevalence of MetS varies by population and is influenced by genetics, ethnicity, sex, lifestyle choices, and socioeconomic factors.^[11] Globally, concerns are rising, particularly in urban areas of developing countries. In Europe, about a quarter of adults have MetS, with similar rates in Latin America^[12] and prevalence in East Asian countries ranging from 8% to 18%.^[13,14] Key risk factors include abdominal obesity, visceral adiposity, and insulin resistance, linked to physical inactivity, aging, sarcopenia, and hormonal imbalances.^[15–17]

Hormonal Changes Associated with Menopause

Hormonal changes during menopause significantly affect physical, emotional, mental, and social well-being. The primary changes involve decreased production of estrogen and progesterone by the ovaries, leading to symptoms such as hot flashes, vaginal dryness, mood swings, sleep disturbances, and alterations in sexual function. Research indicates that these hormonal fluctuations, particularly decreased estrogen and increased FSH levels, may heighten the risk of MetS.^[18] Elevated serum FSH correlates with obesity and osteoporosis post-menopausal, while blocking FSH can reduce body fat and increase bone density.^[19] Increased testosterone and reduced sex hormone-binding globulin (SHBG) levels are linked to components of MetS, such as central adiposity and elevated triglycerides,^[20] with testosterone being a significant factor in MetS incidence.^[21] The loss of estrogen during menopause contributes to metabolic changes that can lead to MetS development. In addition, estrogen affects insulin sensitivity, offering protection against insulin resistance in women with E2-repletion.^[22] Estrogen also supports musculoskeletal health, with its deficiency linked to accelerated bone and muscle loss, further contributing to MetS risk.^[23]

Hormonal Changes Associated with Andropause

Hormonal changes play a significant role in MetS and male hypogonadism. Testosterone deficiency contributes to an increase in visceral adiposity, insulin resistance, and metabolic disorders. The relationship between hypogonadism and MetS is bidirectional and involves complex mechanisms.^[24] Metabolomic studies have revealed alterations in biochemical pathways in individuals with hypogonadism, including compromised glycolysis and stimulated gluconeogenesis.^[25] Andropause, a gradual alteration in sex hormone levels, contributes to the development of MetS. Low testosterone levels, along with low levels of dehydroepiandrosterones (DHEA-s), are associated with MetS in men. Inflammatory markers, such as high-sensitivity C-reactive protein, tumor necrosis factor-alpha, and interleukin-6, are elevated in male hypogonadism, contributing to inflammation and cardiovascular risk. Low SHBG levels, low total testosterone levels, and androgen deficiency are associated with an increased risk of developing MetS, particularly in non-overweight middle-aged men.^[26] Testosterone therapy improves MetS and reduces mortality risk.^[27,28] Further research and clinical trials are needed to strengthen the evidence and validate therapeutic

approaches involving testosterone normalization, caloric restriction (CR), and physical exercise.

Nutrition and dietary practices are critical for optimal aging, as neglect can result in age-related diseases. An integrative approach that combines a healthy lifestyle with a nutrient-dense diet is vital for maintaining homeostasis and preventing chronic conditions. Nutritional interventions, including adequate energy intake, essential nutrients, antioxidants, and phytochemicals, effectively promote healthy aging and mitigate age-associated ailments. Furthermore, the significant role of hormone replacement therapy (HRT), alongside phyto-therapeutic strategies employing various therapeutic herbs, warrants attention. This comprehensive framework not only deepens our understanding but also facilitates personalized interventions aimed at enhancing health and well-being throughout the lifespan. Details of nutrient dosages and outcomes are summarized in Table 1.

Phytoestrogens and Isoflavones

Phytoestrogens, plant-derived compounds mimicking estradiol, are gaining attention for their potential to alleviate menopausal symptoms such as hot flashes, mood changes, and decreased libido due to declining estrogen levels. They are being explored as alternatives to HRT.^[29] Research indicates that isoflavones, particularly from soy and red clover, may reduce the frequency and severity of hot flashes. A meta-analysis of randomized controlled trials (RCTs) showed that oral phytoestrogen interventions improved menopausal symptoms and reduced the Kupperman Index.^[30] In addition, phytoestrogens may alleviate urogenital symptoms and enhance sexual satisfaction. These compounds exhibit weak estrogenic effects and may help prevent conditions linked to estrogen decline, such as cardiovascular diseases and post-menopausal osteoporosis.^[31] However, their efficacy as an HRT substitute is still under investigation, with limited research on their effects in men. Isoflavones may reduce breast cancer risk among Asian women with lifelong soy consumption, though their effects in Western populations remain unclear. Soy intake is linked to modest reductions in low-density lipoprotein (LDL) and total cholesterol levels, with about 25 g of soy protein daily leading to a decrease of approximately 3.2% in LDL cholesterol.^[32] Concerns exist regarding soy isoflavones' potential negative effects on thyroid function.^[31]

In breast cancer, lignans and enterolignans are considered protective, with studies suggesting risk reduction linked to higher fruit and vegetable consumption. Enterolignans act as selective estrogen receptor modulators, affecting

Table 1. Summary of nutraceuticals, their dosages, and associated outcomes

Author, year (reference)	Study design	Study population	Intervention/nutrient	Dosage	Comparator	Outcomes
Blanco Mejia et al., 2019 ^[32]	Meta-analysis	Adult men and women	Soy protein	25 g/daily 6 weeks	Non-soy protein controls	A decrease of approximately 3.2% in LDL-C and total cholesterol
Wang et al., 2023 ^[40]	Systematic review and meta-analysis of RCTs	8,489 adult men and women with MetS and CVDs	Omega 3	≤2 g/day	Control	Favorable effect on improving TG, TC, HDL, SBP, DBP, IL-6, TNF-α, CRP, and IL-1 levels
Tardivo et al., 2014 ^[43]	RCT	87 post-menopausal	Omega 3	900 mg	Control	Significant reductions in BMI, waist circumference, BP, TG levels, IL-6, and insulin resistance
Ferreira et al., 2020 ^[45]	Double-blind, placebo-controlled trial	160 post-menopausal women	Vitamin D	1000 IU/day for 9 months	Placebo	In the intervention group, there was an increase in 25-hydroxyvitamin D (25(OH)D) levels and a decrease in TG, insulin, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Decreased risk of MetS, hypertriglyceridemia, and hyperglycemia compared to the placebo group, who presented a decrease in 25(OH) D and an increase in glucose levels.
Akbari et al., 2018 ^[46]	A systematic review and meta-analysis of RCTs	Patients with metabolic diseases	ALA	200–1800 mg/day 2 weeks–51 weeks	Placebo/control	ALA supplementation significantly decreased fasting plasma glucose (FPG), insulin levels, HOMA-IR, HbA1c, TG, and LDL-C. While no detrimental effect of ALA supplementation on HDL-cholesterol levels
Rahimlou et al., 2019 ^[47]	Systematic review and meta-analysis of RCTs	Patients with cardio-metabolic disorders	ALA	300–1200 mg/day 2 weeks–192 weeks	Placebo/control	Intervention with (ALA) led to significant improvements in fasting blood glucose, TNF-α, IL-6, and CRP with minimum side effects, whereas no significant effects were observed on insulin levels and HOMA-IR
Zamani et al., 2022 ^[49]	A systematic review and dose-response meta-analysis of RCTs	Adults with CVD risk factors	Berberine	0.3–10 g/day 2 weeks–104 weeks	Placebo/control	Supplementing berberine lowered fasting blood glucose and HbA1c levels, as well as promoted weight management, and reduced inflammatory markers

LDL-C: Low-density lipoprotein cholesterol, RCTs: Randomized controlled trials, MetS: Metabolic syndrome, CVD: cardiovascular disease, TG: Triglyceride, TC: Total cholesterol, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IL: Interleukin, TNF-α: Tumor necrosis factor-α, CRP: C-reactive protein, BMI: Body mass index, BP: Blood pressure, ALA: Alpha lipoic acid, HbA1c: Hemoglobin A1c.

the estrogen receptor-alpha (ER α) domain, promoting cell differentiation, and exhibiting anti-proliferative effects. Animal studies indicate enterolactone may reduce mammary tumors in early breast cancer stages. However, more research is needed to clarify enterolignans' preventive effects on prostate and breast cancers. The impact of lignan consumption on LDL and triglyceride levels shows mixed results, with some studies suggesting benefits, but findings remain inconclusive regarding cholesterol markers.^[31]

Bioidentical Hormonal Therapy (BHT) and Phytotherapy

Bioidentical hormonal therapy and phytotherapy present alternative methods to conventional HRT for managing menopausal symptoms. Moreover, BHT has been marketed as a safer, more natural alternative to conventional HRT; however, scientific evidence supporting claims of superior efficacy and safety is lacking, mostly concerning compounded BHTs. While both estrogen therapy and phytotherapy have demonstrated efficacy in alleviating oral discomfort in menopausal women, estrogen is particularly effective for salivary changes.^[33] A systematic review revealed that compounded BHTs were primarily administered at low doses, leading to significant mood improvements but inconsistent results regarding vasomotor symptoms such as hot flashes.^[34] Furthermore, Cochrane reviews of RCTs highlighted that BHT, particularly 17 β -estradiol, was more effective than placebo in reducing hot flashes yet was associated with adverse effects such as headaches and vaginal bleeding. The quality of evidence regarding long-term safety outcomes, including breast cancer and cardiovascular disease, remains low.^[35] As HRT continues to play a role in managing climacteric symptoms, informed decisions should be made by patients and physicians, considering the best available evidence and individual patient needs. Comparatively, phytotherapy encompasses the application of botanical agents for therapeutic purposes, thereby distinguishing itself from conventional pharmacological treatments. As a vital component of complementary and alternative medicine, phytotherapy provides natural interventions for various health conditions, particularly in urology. For instance, Saw Palmetto is frequently employed to alleviate lower urinary tract symptoms in individuals with benign prostatic hyperplasia for its significant anti-inflammatory and antiandrogenic properties, with empirical studies suggesting its efficacy in reducing surgical complications. Similarly, *Urtica dioica* is recognized for its anti-inflammatory effects and capacity to inhibit cellular proliferation.^[36]

Despite the potential benefits of these and other therapeutic plants, there is an urgent need for further research involving human subjects to thoroughly evaluate the associated risks, especially concerning hormone-sensitive cancers, toxicity, and their impact on the endocrine system.

Omega-3 Fatty Acids

Omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, are crucial for overall health and well-being. They play a significant role in protecting against diseases associated with menopause, andropause, and aging by reducing inflammation and enhancing cellular fluidity, essential for bodily functions.^[37] One primary benefit is their ability to lower cardiovascular disease risk by decreasing triglyceride levels and stabilizing cell membranes.^[38] In addition, they improve metabolic health by regulating glycemia and enhancing insulin sensitivity. Omega-3s promote bone health by maintaining calcium balance and reducing inflammation.^[39] In men experiencing andropause, they are linked to better cardiovascular health and may improve testosterone levels.^[40] A favorable omega-6 to omega-3 ratio of 4:1 may lower disease risks, including breast cancer,^[41] and influence testosterone production.^[42] Moreover, a RCT involving 87 post-menopausal Brazilian women found that daily oral supplementation of omega-3 resulted in significant reductions in body mass index, waist circumference, blood pressure, serum triglyceride levels, interleukin-6, and insulin resistance,^[43] suggesting that omega-3 fatty acids may play a protective role against obesity and MetS, particularly in relation to lipid modifications.

Vitamin D

Vitamin D is crucial for metabolic health, primarily aiding in calcium absorption, which is vital for bone integrity. Its role extends beyond bone health; it has been shown to lower glucose levels in pre-diabetic individuals, enhance insulin regulation, and exhibit anti-inflammatory properties. A deficiency in Vitamin D is strongly linked to metabolic disorders such as obesity and type 2 diabetes mellitus, highlighting its importance in preventing cardiometabolic diseases. Ensuring adequate Vitamin D levels is particularly important for populations experiencing menopause and andropause, as it can optimize metabolic function and overall well-being.^[44] A randomized control trial showed that supplementing 1000 IU daily of Vitamin D for 9 months showed a significant decrease in the risk of developing MetS, hypertriglyceridemia, and hyperglycemia compared to placebo.^[45]

Antioxidants and Anti-inflammatory Compounds

Alpha Lipoic Acid (ALA)

ALA has been highlighted in systematic reviews and meta-analyses for its potential benefits in managing glucose control and lipid profiles, particularly among patients with metabolic diseases. ALA supplementation is associated with improved insulin sensitivity, enhanced glucose absorption, and better glycemic control, making it a promising option for individuals with MetS. In addition, ALA has been shown to lower triglyceride and cholesterol levels, contributing to overall cardiovascular health.^[46,47]

Berberine

Berberine, a plant-derived alkaloid, has gained attention for its effectiveness in addressing issues related to estrogen deficiency during menopause. It combats oxidative stress, atherosclerosis, and metabolic disorders such as type 2 diabetes. Research indicates that berberine supplementation can significantly reduce LDL cholesterol, triglycerides, and insulin resistance in menopausal women while also improving mood during the transition.^[48] A systematic review and meta-analysis confirm its benefits in lowering fasting blood glucose and hemoglobin A1C levels, as well as aiding in weight management and reducing inflammatory markers.^[49] Furthermore, berberine exhibits anti-aging properties by activating AMP-activated protein kinase (AMPK), which stimulates longevity pathways.^[50]

Probiotics and Gut Health

The role of probiotics in gut health is crucial, especially concerning menopause-related conditions. Menopause is associated with changes in the gut microbiome, characterized by a decline in beneficial *Lactobacillus* bacteria and an increase in bacteria such as *Sutterella* and *Bacteroides*.^[51] These changes potentially contribute to the development of menopause-related conditions. Probiotic supplementation, particularly with *Lactobacillus* strains, has shown benefits in improving vaginal, bone, and cardiovascular health in post-menopausal women.^[52] The gut microbiome's ability to metabolize estrogens through the estrobolome by the beta-glucuronidase enzyme highlights the importance of maintaining a healthy gut to regulate hormone levels and alleviate menopause symptoms.^[53] In addition, probiotics can enhance glycolipid metabolism and reduce inflammation, positively influencing metabolic health. They have been shown to improve glycemic control and lipid metabolism, which is particularly beneficial for individuals with or at risk of developing MetS.^[54]

Dietary Approaches for Managing MetS

Intermittent Fasting (IF) and CR

A systematic review and meta-analysis indicate that both IF and CR effectively improve cardiometabolic risk factors, weight management, and hormonal balance. IF is particularly beneficial for weight loss, enhancing fat-to-muscle mass ratio, insulin resistance, and menopausal symptoms, although CR may provide greater benefits in some areas. IF can enhance metabolic flexibility, reduce inflammation, and improve mental clarity. In menopausal women, it aids in weight loss and contributes to a healthier hormonal profile while also addressing metabolic changes associated with aging in men.^[55]

Mediterranean Diet (MD)

The MD shows promise in managing MetS during menopause and andropause. A systematic review and meta-analysis links MD to improved skeletal integrity, reduced menopausal symptoms, and better cardiovascular health.^[56] Adherence to this diet is associated with lower adiposity and improved metabolic indices. Its anti-inflammatory properties and neuroprotective elements may also slow cognitive decline. Combining the MD with other healthy lifestyle practices can optimize health outcomes for those at risk of MetS during these transitional periods.^[56]

Low-carb and Ketogenic Diets

Low-carb diets, including ketogenic diets, have been explored for their potential benefits in managing menopause and andropause symptoms. These diets can stabilize blood sugar levels, aid in weight management, and improve metabolic health.^[57] Studies show that ketogenic diets can reduce adipose tissue while preserving lean mass, enhance insulin sensitivity, and create an unfavorable environment for cancer proliferation.^[58] Overall, low-carb diets have effectively reversed MetS, particularly concerning triglycerides and HDL cholesterol.^[59]

Conclusion

The review aims to enhance understanding of managing metabolic disorders related to hormonal changes associated with aging, particularly during menopause and andropause. These life stages are characterized by a progressive decline in reproductive hormones, adversely impacting metabolic health. To address these hormonal imbalances, a comprehensive approach is essential, recognizing the complex interplay between sex hormones and metabolism.

A significant focus is on the role of nutritional intake and the gut microbiome in maintaining metabolic health. Proper nutrition promotes nutrient absorption and utilization while reducing inflammation. The inclusion of antioxidants and anti-inflammatory compounds in the diet is highlighted as beneficial for alleviating metabolic consequences of hormonal fluctuations and combating oxidative stress, and chronic inflammation linked to metabolic dysregulation and aging.

A critical focus should also be placed on hormonal management for both symptomatic and asymptomatic individuals, when necessary, to restore the harmony of bodily systems. This can be achieved through BHT or the use of therapeutic plants as adjuncts in mild cases. However, it is important to note that there is currently no viable consensus or sufficient evidence that can be generalized due to multiple covariates, including risks of allergic reactions, bleeding, thrombosis, cardiovascular events, hormone-sensitive cancers, abnormal tissue growth, toxicity, and other effects on the liver and endocrine systems. However, it is imperative that informed decisions are made by both patients and physicians. These decisions should be grounded in the best available evidence and tailored to individual patient needs.

In addition, this review discusses various dietary interventions effective in managing metabolic abnormalities and hormonal imbalances. Strategies such as IF, CR, and dietary patterns such as Mediterranean, ketogenic, and low carbohydrate diets have positive effects on insulin sensitivity, weight management, and other metabolic markers, all of which impact the steroidogenesis pathways in both sexes. These approaches can be tailored to individual preferences, making them accessible to diverse populations.

In conclusion, the review advocates for a holistic approach integrating essential nutrients, a supportive gut microbiome, antioxidants, anti-inflammatory compounds, and targeted dietary interventions to address the potential for hormonal adjustment therapies. This strategy holds promise for mitigating the metabolic impacts of hormonal imbalances experienced during menopause and andropause, emphasizing further research to optimize these interventions for maximum effectiveness.

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