

The menopausal transition and metabolic disruptions: Unraveling the role of estrogen decline



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Abstract

Menopause associated estrogen decline presents the interplay of the hypothalamic pituitary gonadal axis and estrogen leading to loss of estrogen's protective effects causing significant metabolic challenges marked by glucose homeostasis dysregulation, insulin resistance leading to obesity, increased cardiovascular disorders and non-alcoholic fatty liver disease. Managing these metabolic disruptions require a comprehensive approach using insulin sensitizers, lipid lowering agents, hormone replacement therapy along with the lifestyle modifications involving a well-balanced diet with regular physical activity. While these approaches mitigate these effects, treatment strategies to address concerns regarding the long term safety of the current approaches can improve women's health during this transition.

Keywords: Perimenopause, metabolism, insulin resistance, cholesterol

1. Introduction

Perimenopause also known as menopausal transition is a biological process marking an end of a women's reproductive years caused due to the physiological changes in a female's body primarily driven by hormonal fluctuations (1). The aging of ovary has significant impact on ovarian follicle leading to declined estrogen and progesterone production further influencing the pace of menopausal transition (2). 17β - Estradiol (E2), follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels in the blood vary significantly in the early menopause transition phases considering depletion of oocytes to critical threshold and complicated endocrinology of female reproductive tract (3). Throughout the menopausal transition taking place in female, some subtle changes in the body takes place characterized by irregular menstrual cycles due to unpredicted ovulation, hot flashes which vary in frequency, duration and the intensity, sudden mood swings and irritability often leading to sleep disruption, vaginal dryness (2). Other chronic diseases like atherosclerosis, diabetes, hyperlipidemia, obesity, PCOD are considered to be most prevalent causing decline in the immune functions which influences age related metabolic changes in females. The interplay of declining estrogen levels has profound impact on health leading to metabolic disruptions like altered glucose metabolism, musculoskeletal degeneration, lipid imbalance contributing to high risk of cardiovascular diseases (4-6).

2. Neuroendocrine connection: Estrogen and metabolism

One of the most critical systems orchestrating the balance between the hormonal signals in females is the Hypothalamic-Pituitary-Gonadal (HPG) axis (7). The female reproductive hormones are precisely regulated by hypothalamus, pituitary glands and the gonads working in cohesion thereby regulating the overall reproductive health. The master gland of the body popularly known as the hypothalamus release gonadotropin releasing hormone (GnRH) stimulating release of gonadotropins (LH and FSH) signaling the ovaries to produce estrogen (mainly 17 β estradiol, E2) and progesterone essential for regulating menstrual cycle, follicular development and ovulation to prepare uterine walls for implantation (8). In healthy premenopausal females, the primary site for the production of E2 are the ovaries which circulate in the bloodstream exerting several physiological effects and acting on the target tissues by binding to estrogen receptors (9). Eventually when the female approaches menopause, dysregulation of HPG axis and hormonal fluctuations lead to decline in normal ovarian follicular reserve. The loss of the regulatory influence of estrogen extends to affecting the metabolic health of the females.

2.1. Role of estrogen in regulating female metabolism

2.1.1. Maintain steady glucose levels

Glucose, a monosaccharide sugar, which easily breaks down for releasing energy serves as primary substrate for humans for maintaining cellular functions and overall metabolic health. The food rich in carbohydrates yield glucose when broken down in body adding to daily calorie intake for energy utilization (10). Glucose breakdown occurs by two main metabolic pathways involving glycolysis yielding pyruvate and lactate anaerobically generating small amount energy and citric acid cycle generating energy aerobically in the most efficient way to fuel biological processes (11). As the body continuously utilizes glucose, insulin produced by the β cells of pancreas keep the levels of glucose maintained in blood stream as well as preventing its excess production by liver stimulating glycogen storage. The main role of estrogen in regulating glucose levels is by improving the insulin sensitivity preventing sudden surge in blood glucose levels. Estrogen possessing anti-inflammatory properties, also aid in regulating inflammation and oxidative stress and preventing β cell dysfunction (10-12).

2.1.2. Regulate cholesterol levels

Cholesterol, a steroid alcohol is a lipid produced by the liver essential to maintain cell membrane integrity, hormone synthesis like estrogen, progesterone and testosterone, bile acid production and Vitamin D synthesis (13). Though cholesterol is beneficial to the body, the excess buildup in the body poses risk of cardiovascular diseases. In premenopausal females, as the estrogen levels are high, its cardioprotective effect helps regulate the lipid metabolism thereby lowering low density lipoprotein (LDL) known as the “Bad Cholesterol” by preventing plaque buildup across the arteries caused by lowering its oxidation and the chances of atherosclerosis. On the other hand, estrogen promotes clearing cholesterol from the blood stream by increasing high density lipoprotein (HDL) thereby reducing risk of cardiovascular disease and strokes by promoting nitric oxide production leading to vasodilation, thus reducing arterial stiffness (4,14).

3. Metabolic disruptions during menopausal transition

When a female approaches perimenopause, hormonal fluctuations, alteration in body composition and metabolic changes are observed and one of the most significant concerns primarily observed is the weight gain and obesity (10,15). It is the persistent decline in the estrogen levels that cause shift in the fat storage from subcutaneous (under the skin) to visceral (abdominal fat). Another reason for fat accumulation and obesity is the reduced body's ability to regulate lipids due to low estrogen increasing the risk of low body mass ratio and low fat oxidation giving rise to reactive oxygen species (16). The fat eventually starts accumulating in the arteries with likelihood of developing cardiovascular disease due to atherosclerosis. When the excess fat starts accumulating in the liver in absence of alcohol is Nonalcoholic Fatty Liver Disease which leads to inflammation, fibrosis and cirrhosis which eventually develops to more severe forms like nonalcoholic steatohepatitis (17). Another metabolic disorder associated with low estrogen and obesity is insulin resistance due to the insulin receptors becoming less responsive and overtime developing resistance. In turn, compensatory hyperinsulinemia leads to Type II diabetes (10,18). This condition reduces the glucose uptake into muscles and increased gluconeogenesis.

Table 1. Metabolic disorders associated with low estrogen during menopausal transition

Metabolic disorders	Effect observed	Reference
Obesity	Increase in excess fat, oxidative stress, lipogenesis and body mass index, Decrease in calorie utilization	(10,16)
Cardiovascular disease	Increase in LDL, reactive oxygen species, triglycerides leading to risk of atherosclerosis, Decrease in HDL	(6,9)
Nonalcoholic fatty liver disease	Increase in adipose tissue lipolysis, free fatty acid, fat deposition in liver, and fibrosis	(17)
Type II diabetes	Increase in insulin resistance leading to hyperinsulinemia and hepatic glucose production (hyperglycemia), Decreased sensitivity to GLUT 4 receptors	(10,18)

4. Strategies for managing metabolic disruptions

A multifaceted holistic approach is essential to manage the metabolic syndromes associated with estrogen deficiency focusing on therapies, lifestyle modifications for hormone balance.

Table 2. Detailed strategies to address metabolic disorders associated with perimenopause

Strategies		Ref
Hormone replacement therapy		
Estrogen therapy	- Alleviate perimenopausal symptoms binding to intracellular receptors - Restore balance and eventually mitigate vasomotor symptoms - regulate cardiovascular health - increasing nitric oxide production – vasodilation - Regulate lipid metabolism and glucose levels - Usually given to females undergone hysterectomy	(19)
Combined estrogen-progestin therapy	- Given to females who haven't undergone hysterectomy - Alleviate perimenopausal symptoms - Reduce chances of endometrial cancer (protective effect of progestin)	(20)
Selective estrogen receptor modulators (SERM)	- It intends to target estrogen receptors in selective manner - Prevent osteoporosis, manage menopausal symptoms and improve lipid profile - Prevents breast cancer - Example: Tamoxifen, raloxifen, bazedoxifen, ospemifine	(21)
Pharmacological approaches		
Insulin sensitizers	- Improves body's sensitivity to insulin and lowering blood glucose levels - Biguanides (eg. Metformin) reduce gluconeogenesis, enhance glucose uptake in muscle and fats by amp activated protein kinase pathway. - Aids in weight loss, no hypoglycemia and has cardioprotective action - Thiazolidinediones (eg. Pioglitazone, rosiglitazone) activate peroxisome proliferator-activated receptor gamma – regulate glucose and lipid metabolism by reducing inflammation, oxidative stress, improving lipid profile and enhancing β cell function - Increase insulin sensitivity by promoting glucose uptake, shift visceral fat to subcutaneous fat - For type ii diabetes, pcos, nonalcoholic fatty liver disease - Other insulin sensitizers include - Glucagon like peptide 1 (eg. Exenatide, semaglutide, dulaglutide) that reduce blood sugar and energy intake. - Sodium glucose cotransporter-2 (eg.Dapagliflozin, sotagliflozin, empagliflozin) that promotes weight loss by improving insulin sensitivity.	(22)
Lipid lowering agents	- Statins (eg. Atorvastatin, rosuvastatin) inhibit HMG CoA reductase – decrease LDL and triglycerides, increase HDL - Primary therapy to treat hypercholesterolemia and reduce cardiovascular disorders - Ezetimibe inhibits intestinal cholesterol absorption and is adjunct to statin intolerant patients - Bile acid sequestrants (eg.Cholestyramine) prevent bile acid intestinal reabsorption - Fibrates (eg. Fenofibrate, gemfibrozil) activate peroxisome proliferator-activated receptor alpha increasing lipolysis and reduce triglyceride production - Main therapy in hypertriglyceridemia, reduce LDL	(23)

Lifestyle modifications		
Nutritional interventions	- Phytoestrogens are plant compounds with mild estrogenic effects to balance hormones - Food source: flaxseeds, chickpea, lentils - Vitamins and minerals like calcium, magnesium, vitamin d, vitamin b are essential for bone health, reduce mood swings, help with sleep, boost metabolism	(24,25)
Physical activity and exercise	- The benefits include maintaining cardiovascular health, bone mineral density, sleep quality, immunity - Also reducing the risk for PCOD, type II diabetes, cholesterol	(26)

5. Conclusion

The extensive research on the role of estrogen in metabolic syndromes associated with menopause and perimenopause underscores significant concerns and challenge in women's healthcare. The role of current approaches and interventions offer potential solutions, but it is essential to scrutinize its long term efficacy and safety in individuals. Additionally physical activities and certain lifestyle changes pertaining to diet can pave the way for an improved health during menopausal transition phase. However, the development of advanced delivery systems could help in multidisciplinary approach which would be instrumental in optimizing menopausal health and mitigating the metabolic disruptions

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