REVIEW ARTICLE

An Update on Gut Microbiome and Postmenopausal Health with Clinical Implications

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Received on: 25 September 2023; *Accepted on:* 24 November 2023; *Published on:* 23 February 2024

Abstract

The decline of estrogen levels in postmenopause triggers significant health changes. Recent insights reveal a dynamic link between gut microbiome and estrogen, suggesting combined influence on postmenopausal health care. Reduced gut microbiome diversity is a sign of intestinal dysbiosis, linked with aging, western lifestyle, and a number of illnesses conditions. Several physiological reactions are changed when dysbiosis develops in postmenopausal state which contributes to the illness states obesity, metabolic syndrome, cancer, osteoporosis to name a few. Investigating the interplay between gut microbiota and estrogen deficiency holds promise for enhancing postmenopausal well-being and health outcomes.

Keywords: Cancer, Estrobolome, Gut microbiome, Obesity, Osteoporosis, Postmenopausal women, Type 2 diabetes.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2402

Introduction

Menopause signifies the end of a woman's reproductive cycle with a gradual decrease in ovarian activity along with a physiological impairment of hypothalamic–pituitary–ovarian axis function associated with altered hormone levels resulting in menopausal syndrome.[1] These negative health consequences are thought to be caused directly by the decline in ovarian sex hormones, especially estradiol. In addition to having a negative impact on a person's life quality, menopausal symptoms can increase a patient's risk of developing diabetes, osteoporosis, breast cancer, and cardiovascular disease.[2,3] Recent research has also revealed a link between gut bacteria and metabolic disorders in postmenopausal women. These steroid hormones are regarded to preserve the gut barrier and protect against gut injury.[4]

The microbiota relates to the huge population of microbial organisms located on and inside the body, including fungi, viruses, and bacteria.[5] The human gastrointestinal system is a habitat to over 100 trillion microbes, which is better described as one of the virtual organs of the body.[5] The gut microbiota processes food components (such as fiber, amino acids, and hormones) and endogenous chemicals (such as bile acids) in a way that may reduce the risk of metabolic syndrome. Whereas other bacterial metabolites and cell wall constituents could serve as a factor in low-grade inflammation and insulin resistance.[6]

Numerous summaries regarding the connection between gut microbiota and metabolic illnesses have so far been published. There is still much to learn about the vital role that gut bacteria metabolites play a role in postmenopausal phase pathogenic disorders; hence, a thorough and timely description is required. With a focus on the underlying mechanism, this review intends to critically evaluate the potential contribution of gut metabolites to pathological conditions in postmenopausal state.

Materials and Methods

The following terms were used to go through different scientific literature on PubMed/Medline or Google Scholar. Estrogen, gut microbiome, menopause, postmenopausal obesity, obesity, Type 2 diabetes, osteoporosis, cancer and estrobolome etc. Peer-reviewed, English-language original papers that were indexed in PubMed were included. To thoroughly evaluate the literature on association between the gut microbiota and estrogen levels, publication dates.

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How to cite this article: Alva P, Rai S, Naresh S, *et al*. An Update on Gut Microbiome and Postmenopausal Health with Clinical Implications. J South Asian Feder Obst Gynae 2024;16(2):150–155.

Source of support: Nil

Conflict of interest: None

Estrobolome: Interplay of Gut Microbiome and Estrogen

Dysbiosis is indicated by decreased gut microbiome diversity associated with aging, western lifestyle, and several illnesses conditions.[7] Hippocrates a father of modern medicine said "Every disease originates in the gut." Numerous studies supporting this idea have been conducted during the last two decades. Dysbiosis has been demonstrated to impair the functioning of the gut epithelial barrier by decreasing cell–cell interactions, which then causes increased permeability and bacterial translocation.[8] Inflammatory and metabolic diseases are caused by the leakage of gut-derived pathogen-associated chemicals and toxic substances into the blood circulation when the delicate equilibrium at the mucosal interface is disturbed.[9]

Certain bacterial species have active beta-glucuronidase and colonize the human gut which can convert conjugated

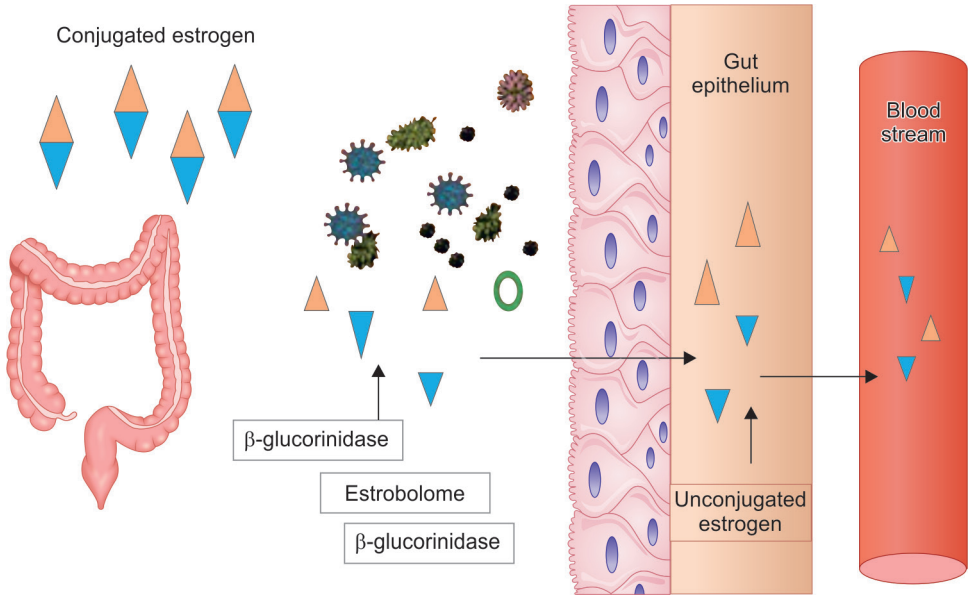

Fig. 1: Circulating estrogens are significantly regulated by the microorganisms in the gut. The "estrobolome" of these estrogen-metabolizing bacteria releases an enzyme called glucuronidase that degrades conjugated estrogen, allowing estrogen to be reabsorbed by the stomach and transported into the circulation

estrogens into deconjugated analogues. This lowers the rate at which estrogens are eliminated from the body and increases the reabsorption of estrogens into the blood.[10] As a result, intestinal and distal mucosal homeostasis is regulated by the gut microbiota.[11] These estrogens function as follicular stimulators, boosting bone density, cardiovascular protection, etc. by binding to receptors. Thus, the gut microbiota is a possible biomarker for diagnosing and preventing diseases linked to estrogen. Therefore, several physiological reactions are changed when dysbiosis develops in the postmenopausal state which contributes to the illness states described below (Fig. 1).

Estrogens and Microbiota Interactions in Pathological Conditions

Obesity and Type 2 Diabetes (T2D)

Obesity, metabolic syndrome symptoms are much more common in postmenopausal women. The decreased estrogen levels seen in postmenopausal women may be a major contributor to obesity. Obesity alters functions of the gut microbiome. Independent of one another, the microbiota and estrogens both play important roles in obesity. A study of metabolic function of the gut microbiota in mice has shown that nutrition significantly influences the makeup of the microbiota rather than only obesity.[12] The health and function of the epithelial barrier are significantly influenced by butyrate, a vital vitamin in the gut.[13] In a study using mouse models—one prone to obesity and the second resistant to it, function of butyrate was examined to determine how food affected the gut microbiota.[12] To examine the function of microbial butyrate metabolism, the number of genes (butyryl-CoA transferase-related genes) in the gut microbiota that can metabolize items into butyrate was counted.[12] Obese mice with higher levels of butyryl-CoA transferase-related genes in their gut microbiome than obese mice with lower levels of these genes are less likely to become obese.[12] Gordon and co-workers report support that the gut microbiota is important in modulating host obesity. Whereas germ-free (GF) mice generally had less body fat than conventionalized specific pathogen-free (SPF) mice, despite eating more and using less energy.[13] Thus, the pathogenesis of obesity is impacted by the intestinal microbiota in a structure-dependent way. Beta-glucuronidase enzyme affects estrogen metabolism by deconjugating estrogen and phytoestrogen and making them accessible in the circulation upon absorption by the gut. Free estrogen acts on its receptor thereby regulating blood glucose level.[11] Lack of estrogen causes a significant increase in blood cholesterol, obesity, and expression of genes for lipogenesis while decreasing the abundance of the genera *Akkermansia* and *Bacteroidetes*, indicating that estrogen plays a significant role in obesity, glucose, and lipid homeostasis by regulating intestinal microbiota.[14]

The postmenopausal phase is thought to be a phase of diabetes, mainly caused due to the depletion of estrogen and reported as an active diabetic vigilance period.[11] Estrogen deficiency promotes fat storage, which alters lipid metabolism, resulting in high triglycerides and free fatty acids. Triglycerides and fats in non-fatty tissues disrupts insulin signaling and beta-cell thereby causing insulin resistance.[11] It was observed that the high levels of circulating insulin associated with the obesity phenotype increased gut permeability, permitting bacterial toxins like lipopolysaccharides (LPS) to enter into the bloodstream and triggering a series of inflammatory responses, elucidating the subclinical inflammation seen in obese and insulin-resistant patients.[15]

Studies on T2D have revealed that short-chain fatty acid (SCFA) production, notably butyrate, is reduced, resulting in low-grade inflammation. Low-grade inflammation is often related with the development of T2DM. Complex carbohydrates generated from dietary fiber are broken down by bacterial glycoside hydrolases to create SCFAs, such as acetate, propionate, and butyrate.[16] Short-chain fatty acid producers, such as *Bifidobacterium*, *Faecalibacterium* and *Alistipes*, have been found in postmenopausal gut microbiota.[17] Short-chain fatty acids stimulate skeletal muscle glucose absorption through a glucose transporter protein GLUT418. Reduced SCFAs have a negative impact on the signal transduction associated with T2D such as dyslipidemia and glucose utilization.[18]

Multiple mechanisms explain how SCFAs alter the host's metabolism. It results in the production of peptide YY, an intestinal hormone that inhibits gut motility, accelerates transit through the gut, and reduces absorption of energy from food by the activation of G-protein-coupled receptor 41 (Gpr41) by SCFAs.[19] It has been demonstrated that the incretin hormone glucagon-like peptide 1 (GLP-1) increases the sensitivity to insulin by triggering the activation of G-protein-coupled receptors 43 (Gpr43) and 41 by short-chain fatty.[20] By lowering lipolysis and blocking inflammatory signaling, butyrate may be able to reduce inflammation caused by adipocyte interaction and macrophages.[21] In addition, butyrate decreases the formation of monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), nuclear factor kappa-B (NF-κB) function. Similar to this, propionate was shown to reduce inflammation in adipose tissue and greatly reduced the levels of a significant amount of inflammatory cytokines and chemokines, including TNF-α and CC chemokine ligand.[20] Dysbiosis and alterations in SCFA production in the gut microbiota impair the epithelial barrier and tight junction function, increasing the gut microbiome's translocation into the circulation releasing poisonous by-products such as LPS causing the condition known as leaky gut syndrome and inflammation.[22] The stimulation of the innate immune pathway is one of the probable mechanisms for pro-inflammatory cytokine production in obesity and Type 2 diabetes.

Estrogens lower LPS-induced inflammation via regulating inflammatory pathways by lowering the amount of harmful microorganisms.[22] *In vitro* study demonstrated that the NF-κB signaling pathway and generation of tumor necrosis factor (TNF) triggered by lipopolysaccharide (LPS) are both inhibited by pretreating human macrophages with E2.[23] Additionally, estrogen has been demonstrated to increase synthesis and stop the breakdown of the endogenous NF-κB inhibitor IκB-α.[24] On the other hand, prolonged *in vivo* exposure of murine macrophages to E2 results in an increase in the production of inflammatory cytokines.[24] Thus, direct hormonal action together with menopause that causes gut dysbiosis are likely to result in obesity and diabetes.

Osteoporosis

Menopause onset is a significant risk factor for postmenopausal primary osteoporosis.[25] Recently, it was reported that bone homeostasis is related to intestinal flora.[26,27] The gut microbiome aids the dissociation macromolecules into simpler parts facilitating proper metabolism of bone[28] which effectively reduces osteoporosis and promotes bone density. Additionally, studies have demonstrated that the gut's pH level is essential for nutrient absorption, particularly calcium absorption, can be impacted by the diversity of the gut microbiomes.[29] Short-chain fatty acid propionic acid (C3) and butyric acid can cause osteoclasts to undergo metabolic remodeling, oxidative phosphorylation in glycolysis, and decreased expression of osteoclast-related genes such TRAF6 and NFATc1[30] causing the decrease of bone resorption and the suppression of osteoclast differentiation.

The immune system is regulated by estrogens, and the substances they produce have significant impacts on bone cells. Proinflammatory cytokines have been linked to the onset of bone loss following estrogen discontinuation, according to early investigations in mice and humans. In the absence of estrogen, CD4+ T cells become more activated and produce more inflammatory substances and osteocytic substances, such as

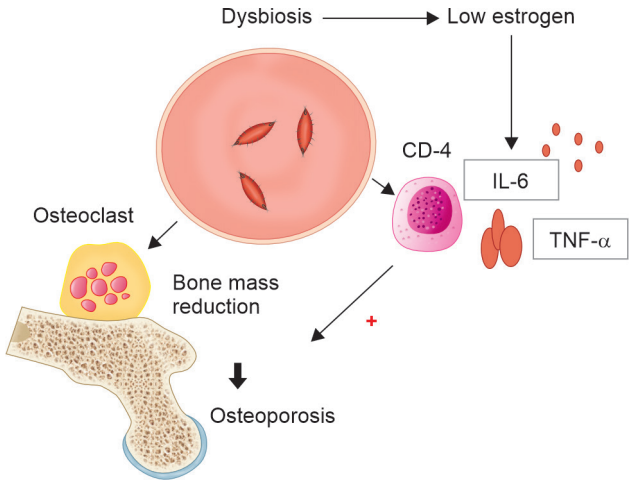

Fig. 2: Gut microbiome can affect bone health through several mechanisms. Low estrogen levels brought on by dysbiosis cause CD4+ cells to become more active and produce more inflammatory and osteogenic chemicals. This promotes osteoclast activity, which reduces bone density and causes osteoporosis in postmenopausal women

TNF-α, IL-1, IL-6, and RANKL[31–33] reduction in intestinal permeability brought by estrogen deprivation causes inflammatory reactions and encourages the production of osteoclasts, which might result in bone loss.[34] Studies have demonstrated that GF mice have higher trabecular bone mineral density (BMD) than mice that were grown normally. Bone mineral density become reduced when GF mice were recolonized with typical intestinal bacteria, suggesting that the intestinal microbiome is involved in the control of bone mass (Fig. 2).[35]

Gut Microbiota and Gynecological Cancer

Among the non-communicable diseases, cancer ranks first as a major contributing factor of morbidity and mortality. The most prevalent kind of gynecological cancer in women is breast cancer, whereas cervical cancers are fourth in prevalence.[36] Among the total cancer cases in India, 39.4% was contributed by breast and cervical cancer.[37] Incidence rates of ovarian cancer are increasing at an alarming rate.[38] The significant shift in the cancer pattern has been noted. The cervix was the leading site of cancer during 1990s, but recently breast cancer has surpassed it as a leading site in most of the cancer registries in India, although cervical cancer is still most prevalent in rural India,[39] the etiology and mechanism of gynecological cancers are not elucidated. Early cancer screening and prevention are extremely important because of the serious threat that cancer poses to human health and the economic toll that it has on people.[40] Research on the gut microbiota and how it relates to human health has been in limelight in the recent years. Dysbiosis, characterized by alteration in gut microbiota composition and function, leading to low-grade inflammation of the mucosal barrier is evidenced to play a major role in causing gynecological cancers. It may also hinder the response of the tumor to treatment; hence, it is crucial to preserve the equilibrium of the intestinal microbiota.[41]

Gut Microbiome and Breast Cancer

Dysbiosis may influence the process of oncogenesis and tumor growth, the response of the antitumor drugs, and its toxicity effects. Although the relation between gut microbiome with breast cancer

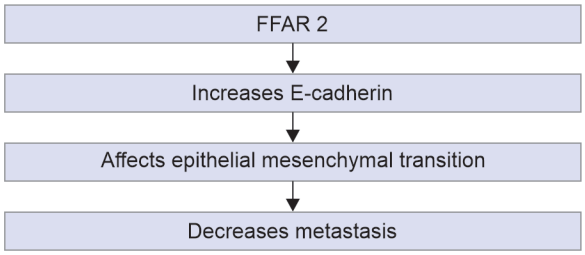

Fig. 3: Role of FFAR 2 in cancer

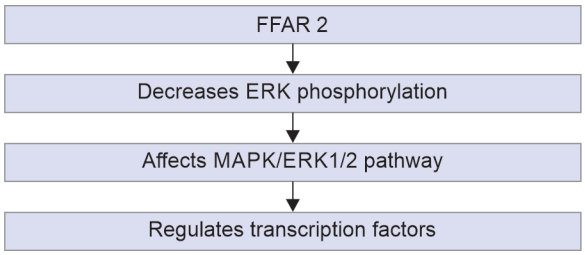

Fig. 4: Role of FFAR 2 in cancer

has not been clearly elucidated, a few steps of this remarkable interplay can be perceived.

The gut microbiota can be viewed as a gland that secretes metabolites that have paracrine and systemic effects. Metabolites may be crucial in controlling several parts of the individuals biological process involving elements that make up the "Hallmarks of Cancer." Procarcinogenic activity of microbiota can be increased simply by the cancer microenvironment.[42]

Effects of Gut Microbiome on Breast Tissue as a Metabolite Secreting Gland

The gut microbiota's metabolism and release of hormone-like bioactive compounds, such as reactivated estrogens, active phytoestrogens, SCFA, lithocholic acid (LCA), and cadaverine, influences the risk of breast cancer. The gut microbiota has a significant impact on the metabolism of estrogen and their metabolites.

A pilot study reported in 48 postmenopausal breast cancer patients, pretreatment, and controls showed that breast cancer in postmenopausal women is linked with disrupted intestinal microbiota composition and estrogen-independent decrease diversity of their gut microbiota.[43] Dysregulation of estrogen metabolism-gut microbiota axis may be regarded as a possible mechanism for increased risk of hormone-dependent breast cancer, making interventions with prebiotics, and probiotics one of the treatment modalities in the future.

Role of Fatty Acids and Fatty Acid Receptors

By regulating cell proliferation and causing apoptosis, FFAR2 and FFAR3 may contribute to the suppression of tumors (Figs 2 to 4).

Role of Bile Acids in Breast Cancer

Lithocholic acid, a secondary bile acid produced from cholesterol has an antiproliferative effect. Seven alpha/beta-hydroxy steroid dehydroxylate present in anaerobic bacteria of Clostridiales converts cholesterol to LCA, which acts on Takeda G-protein-coupled receptor–5 (TGR-5) and inhibits epithelial–mesenchymal transition decreases the tumor spread.[44] It was demonstrated in another study that LCA decreased the multiplication of breast cancer cells, with no effect on normal cells.[4]

Gut Microbiome and Ovarian Cancer

Alterations in the microbiome, termed oncobiosis are considered to play a significant role in the development of ovarian cancer in recent years. Microbiome promotes inflammation and controls immune responses to enable ovarian cancer carcinogenesis.[45]

Role of Bacterial Metabolites on Ovarian Cancer

Lipopolysaccharides

Lipopolysaccharide a component of gram-negative bacteria, stimulates TLR-4 and TLR-2 receptors. Ovarian cancer is linked with a rise in the levels of LPS, driving inflammation.[46] Cancer cells and tumor-associated macrophages can be activated by LPS. When ovarian cancer cells are stimulated by LPS, this results in the upregulation of phosphatidyl-inositol-3 kinase, EMT, and migration of N-cadherin, Snail, Vimentin, TCF, MMP2, MMP9, α-SMA, Slug When Tumor-Associated Macrophages (TAM's) are stimulated by LPS, the macrophage is pushed toward the M1 profile, which is cytotoxic and cytostatic for ovarian cancer cells.[47]

Lysophospholipids

Lysophospholipids are produced in the cells of the host and are involved in the homeostasis of bacterial membranes.[48] Gram-negative bacteria have a higher amount of lysophospholipids and ovarian cancer is linked with a rise in the levels of gram-negative bacteria. Lysophosphatids affect several cancer-related traits, which in turn affect how ovarian cancer cells behave. Lysophosphatidic acid (LPA) and lysophosphatidylserine stimulate Akt, MAPK, and calcium signaling, and LPA stimulates cancerous ovarian cells' cell division, invasion, and migration. In ovarian cancer, LPA can rise the expression of angiogenesis-related genes.[49]

Short-chain Fatty Acids

Acetate, propionate, butyrate, and lactate are examples of SCFAs, which have been shown to have cytostatic effects on a variety of malignancies. Free fatty acid receptors (FFAR) and aryl hydrocarbon receptor (AHR) are acted upon by SCFAs.[50] Fatty acids provide energy and decrease histone deacetylation thus modifying the epigenetic mechanism.[51]

Secondary Bile Acids

Deoxycholic acid, lithocholic, and deoxycholic acid are secondary bile acids produced from primary bile acids by bacterial transformation. The enterohepatic circulation of bile acids is affected and bile reabsorption is altered in ovarian carcinoma.[52]

Gut Microbiome and Cervical Cancer

Growing data suggest that the cervicovaginal and gut microbiota has a role in HPV-related gynecologic cancers. The gut microbiota in eight women with cervical cancer and five healthy individuals was compared by Wang et al.[51] Although this difference was not statistically significant, greater gut microbiota alpha-diversity was seen in women with cervical cancer. Activation of pattern recognition receptors (PRRs) and the inflammatory response caused by microorganism-associated molecular patterns (MAMP) are believed to play a role in gut microbiome-induced tumorigenesis. The host epithelial cell's intracellular signaling pathway induced transcription of antibacterial proteins in response to a MAMP

binding to a PRR (such as a Toll-like receptor). Additionally, the expression of pro-inflammatory cytokines, such as IL-17, TNF-α, and IFN-γ was increased. Modulation of enterohepatic circulation of estrogen by gut microbiota is known to play significant role in cervical cancer.[53]

Our knowledge of the human microbiota has improved because of developments in bioinformatics and microbiome sequencing technologies.[54] The most popular technique is 16S ribosomal RNA (rRNA) amplicon sequencing.[55] However, to thoroughly explore the function of the human microbiome in HPV carcinogenesis, future research must employ whole-genome shotgun sequencing as a complementary option in addition to the more economical 16S rRNA method.

Conclusion

Understanding the complex interplay between postmenopausal health and gut microbiome holds the potential for targeted interventions and personalized approaches to optimize health outcomes for postmenopausal women. Further research is needed to unravel the intricate mechanism underlying this relationship and to develop effective strategies for promoting gut health and overall well-being in postmenopausal individuals.

Acknowledgment

The authors would like to thank NITTE (Deemed to be University).

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