Menopause, the gut microbiome, and weight gain: correlation or causation?

Sarah L. Becker, BA, and JoAnn E. Manson, MD, DrPH, NCMP

Abstract

The gut microbiome is a key regulator of metabolism and influences the metabolism of estrogens, however, the microbiome’s role in the changes in body composition and metabolic risk factors experienced by menopausal women remains largely unexplored. Menopause has been shown to alter the gut microbiome, and rodent studies suggest that microbiome changes postovariectomy are associated with increased adiposity, decreased metabolic rate, and insulin resistance, changes attenuated by estrogen administration. Given these data, a deeper understanding of the gut microbiome’s relationship to menopause-induced changes in body composition and metabolism is warranted and may offer opportunity for novel therapeutic interventions.

The microbiome is central to both systemic and estrogen metabolism, and is altered by the menopausal transition, suggesting an important role of the microbiome in the increased metabolic risk faced by menopausal women. Although additional research is needed to establish a causal link, the interrelationship between menopause and the gut microbiome may represent a new frontier to address menopause-related metabolic risk.

Key Words: Enterohepatic – Estrobolome – Menopause – Metabolic syndrome – Metabolism – Microbiome.

Estrogens are essential hormones in regulating metabolic status in premenopausal women. The decline in estrogen levels during and after the menopausal transition is often accompanied by a reduction in the metabolic rate, an increase in central adiposity, and a higher prevalence of metabolic syndrome risk factors. Higher body mass index and adiposity are also associated with increased prevalence of vasomotor symptoms, one of the primary menopause-related reasons women seek care. With the number of women over 50 years of age continuing to rise due to increased life expectancy, understanding how to treat, manage, and prevent adverse consequences of the menopausal transition is increasingly important.

The microbiome is known to contribute to obesity and metabolic syndrome, and transfer of microbial content from a healthy donor to an obese recipient is able to abrogate these conditions in both mice and humans. Menopause has been shown to alter the gut microbiome as well, leading to decreased microbial richness and diversity. In obese postmenopausal women, several bacterial species have been identified which are associated with metabolic risk factors even after covariate adjustment for age, body fat, and diet, suggesting a causal role of the microbiome in the development of obesity-related metabolic disease. Furthermore, estrogen has been shown to increase gut epithelial integrity, and menopause-induced estrogen deficiency may lead to an increase in epithelial permeability and bacterial translocation, contributing to systemic inflammation, implicated in the development of obesity and metabolic syndrome.

Rodent studies provide additional insights into the potential role of the microbiome in menopausal weight gain and metabolic syndrome. Ovariectomized rats tend to eat more and gain more weight than sham controls, an effect which is attenuated by estrogen receptor agonists. Ovariectomy in rodents is also associated with a shift in the microbiota, with an increased ratio of the phyla Firmicutes and Bacteroidetes in ovariectomized rats compared to sham nonovariectomized controls. In particular, menopause-induced obesity produces unique changes to the composition of the gut microbiome with differential changes in gene expression of estrogen signaling pathways and metabolic pathways in mice who undergo ovariectomy. In this study, which compared the effect of diet-induced versus ovariectomy-induced obesity on the gut microbiota, ovariectomized mice displayed a decrease in the number of bacteria and in alpha diversity compared to control animals who underwent a sham procedure. High-fat diet feeding...
resulted in a similar microbiota composition to that of animals who underwent ovariectomy with the exception of an increased abundance of Bifidobacterium animalis solely in ovariectomized animals, a species correlated with the expression of female hormone metabolism genes.10

Similarly, gut microbiome diversity is protected by low-dose estrogen supplementation in ovariectomized rats and prevents the onset of menopause-associated weight gain, decreased daily energy expenditure, impaired glucose tolerance, and insulin resistance.24 In a study by Park and Kim et al, ovariectomized rats displayed a decrease in microbial richness which was prevented by low-dose intracerebroventricular estrogen administration. Comparisons of bacterial distribution by principle coordinate analysis showed ovariectomized animals clustered separately from those who received estrogen (17β-estradiol or conjugated equine estrogens), or controls who underwent sham ovariectomy surgery, suggesting a difference in the diversity of ovariectomized animals compared to those who received hormone therapies or who were not menopausal.24 No major differences in effect on microbial diversity were observed between estrogen formulations. Additionally, estrogen supplementation was shown to reduce vasomotor changes including a reduction in tail vein temperature, a proxy for hot flashes, and conferred a nonsignificant benefit to memory function.24 Other rodent studies support this work, finding that estrogen supplementation in the form of 17β-estradiol modifies the gut microbiome, with changes associated with a decreased susceptibility to metabolic syndrome.23 Taken together, this suggests estrogen exerts an effect on the gut microbiome concurrent with a reduction in the metabolic and vasomotor changes associated with declining estrogens during menopause.

Is the interplay between estrogen and the microbiome bidirectional, with the microbiome itself regulating estrogen metabolism? Estrogen is primarily metabolized in the liver where it is hydroxylated and conjugated before being excreted in the bile to enter the enterohepatic circulation.25-27 Once in the distal gut, estrogens in the bile are deconjugated by bacterial enzymes allowing for reabsorption through the mucosa and subsequent re-entry into the systemic circulation.28-32 The primary deconjugators of enteric estrogens are bacterial β-D-glucuronidases, which decrease fecal estrogen excretion. It has been estimated that between 33% and 50% of circulating estrogens are incorporated into the bile, with up to 80% of these estrogens then reabsorbed into the intestinal tract.30,33 Such reabsorption is thought to extend the activity of these estrogens in the body, leading to increased serum levels of estrogen metabolites.34

The gut microbiome modulates this system through the estrobolome, the specific intestinal microbes in the gut that encode for enzymes capable of deconjugating estrogens28 (Figure 1). Dietary compounds may also bind directly to estrogen receptors in the gut lumen, regulating target genes through transcriptional activation or repression, and influencing intracellular signaling pathways as well as nongenomic activity through receptor binding in the plasma membrane and

![Eubiosis and Dysbiosis Diagram](image-url)
second messenger signaling. Gut microbial diversity is correlated with high levels of urinary estrogen metabolites (Figure 1). Perturbing the gut microbiota through administration of antibiotics has been shown to decrease urinary estrogen metabolites and increase fecal estrogen excretion by 18-fold, indicating a reduced capacity of a dysbiotic gut microbiota for deconjugation and resulting in conjugated estrogens being excreted in the feces instead of being reabsorbed into enterohepatic circulation. This study was performed in pregnant women, suggesting a need for the study of this process in menopause and other life stages. However, changes to the microbiome due to menopause are supported by observations of decreased enterohepatic estrogen recycling among women who are infertile due to endocrine causes and who excrete lower urinary levels of estrogen metabolites compared to fertile women. Additional research is needed to understand the effect of menopause-related endocrine deficiencies specifically on enterohepatic circulation and on the estrobolome’s capacity for deconjugation. Moreover, there is likely substantial interindividual variation in the activity of bacterial enzymes responsible for deconjugation, which combined with differences in diet, body weight, and other factors affecting the microbiome, may contribute to differences in menopause-associated changes in body composition, adiposity, and risk of metabolic syndrome between individuals.

Given emerging evidence for a role of the microbiome in regulating both adiposity and systemic estrogen levels, understanding how the microbiome can be utilized in a therapeutic capacity during and after the menopausal transition is of great clinical interest. A start may be what we feed our bodies and thus, our microbiomes. Diet has been shown to be a stronger driver of microbiome composition than adiposity or estrogen levels and can be easily modified through food choices. An example is higher intake of dietary fiber, which has been shown to exert a protective effect on intestinal mucosal integrity and risk of obesity in rodent models. In addition to its effects on gut and metabolic health, diet can also serve as a source of phytoestrogens, such as the naturally occurring isolflavones found in soy products, as well as the lignans and coumestans found in legumes, cereals, and flaxseeds (Figure 1). A favorable association of phytoestrogen consumption with lower levels of adiposity and lower prevalence of metabolic syndrome has been noted observationally, including recent studies suggesting soy-based isolflavone consumption reduces body weight and fasting glucose levels in postmenopausal women. Isolflavones act as weak estrogens and are known to produce a similar b-D-glucuronidase activity, and prebiotics high in fermentable fibers are able to improve some markers of metabolic health. Prebiotic administration in rats has been shown to reduce weight gain after ovariectomy, decrease fat oxidation, and improve glucose tolerance, as well as reduce vasoconstriction changes. Such studies are promising, but additional research is needed to understand how the microbiome to improve metabolic health in menopausal women and warranting further investigation is the use of oral pre- or probiotic treatments. Specific strains of probiotics have been shown to modulate b-D-glucuronidase activity, and prebiotics high in fermentable fibers are able to improve some markers of metabolic health. Prebiotic administration in rats has been shown to reduce weight gain after ovariectomy, decrease fat oxidation, and improve glucose tolerance, as well as reduce vasoconstriction changes.

We propose that the interrelationship between menopause, the gut microbiome, adiposity, and metabolic health is an exciting new frontier that warrants further study. The interplay of these systems suggest an opportunity for future clinical interventions such as pre- or probiotic therapy or dietary modifications to support and enhance the gut microbiota during and after the menopausal transition, although additional research into the estrogen-gut axis is needed to establish causality. We encourage further research to better understand the role of the microbiome in the menopausal transition and as an untapped resource that may have preventive and therapeutic potential.

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