Maturitas 103 (2017) 45–53

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Estrogen–gut microbiome axis: Physiological and clinical implications

James M. Baker[a,b,1], Layla Al-Nakkash[c], Melissa M. Herbst-Kralovetz[a,d,*]

[a] Department of Basic Medical Sciences, College of Medicine-Phoenix, University of Arizona, Phoenix, AZ, USA
[b] Department of Biology and Biochemistry, University of Bath, Bath, UK
[c] Department of Physiology, Arizona College of Osteopathic Medicine, Midwestern University, Glendale, AZ, USA
[d] Department of Obstetrics and Gynecology, College of Medicine-Phoenix, University of Arizona, Phoenix, AZ, USA

ARTICLE INFO

Keywords:
Estrobolome
Phytoestrogen
Dysbiosis
Cancer
Fertility
Metabolic syndrome

ABSTRACT

Low levels of gonadal circulating estrogen observed in post-menopausal women can adversely impact a diverse range of physiological factors, with clinical implications for brain cognition, gut health, the female reproductive tract and other aspects of women's health. One of the principal regulators of circulating estrogens is the gut microbiome. This review aims to shed light on the role of the gut microbiota in estrogen-modulated disease. The gut microbiota regulates estrogens through secretion of β-glucuronidase, an enzyme that deconjugates estrogens into their active forms. When this process is impaired through dysbiosis of gut microbiota, characterized by lower microbial diversity, the decrease in deconjugation results in a reduction of circulating estrogens. The alteration in circulating estrogens may contribute to the development of conditions discussed herein: obesity, metabolic syndrome, cancer, endometrial hyperplasia, endometriosis, polycystic ovary syndrome, fertility, cardiovascular disease (CVD) and cognitive function. The bi-directional relationship between the metabolic profile (including estrogen levels) and gut microbiota in estrogen-driven disease will also be discussed. Promising therapeutic interventions manipulating the gut microbiome and the metabolic profile of estrogen-driven disease, such as bariatric surgery and metformin, will be detailed. Modulation of the microbiome composition subsequently impacts the metabolic profile, and vice versa, and has been shown to alleviate many of the estrogen-modulated disease states. Last, we highlight promising research interventions in the field, such as dietary therapeutics, and discuss areas that provide exciting unexplored topics of study.

1. Introduction

The impact of the gut microbiota, and bacteria that reside on other mucosal sites, on health has become a rapidly growing and exciting area of research over the last 10 years. The functional relevance of the bacteria that compose the gut microbiome has been demonstrated in probiotic, fecal-microbiome transplant (FMT) and bariatric surgery studies [1–3]. The impact of the gut microbiome extends beyond the gut through the inflammatory and metabolic changes induced by the gut microbiome [4,5]. Similarly, the host microenvironment of the gut influences the gut microbiome [6]. The gut microbiome has been shown to be influenced by estrogen, however, the gut microbiome also significantly impacts estrogen levels [7,8]. The gut microbiome impacts estrogen levels in the host through the secretion of β-glucuronidase, an enzyme which deconjugates estrogen, enabling it to bind to estrogen receptors and leading to its subsequent physiological downstream effects [9]. It is only the unbound, free estrogen that is biologically active. Most conjugated estrogen is bound via a glycoprotein sex hormone binding globulin (SHBG) produced by the liver [10] with low SHBG levels being implicated in the development of metabolic syndrome [11]. It is widely accepted that estrogen plays a significant role in many disease states including gynecologic conditions and cancers in addition to less obvious estrogen-mediated diseases such as metabolic syndrome (Fig. 1) [12–17]. This review will demonstrate the influence the gut microbiome has on estrogen, and therefore estrogen-mediated disease, and related health outcomes (Fig. 1).

2. Methods

A search of the scientific literature was conducted using PubMed/Medline or Google Scholar using the following search terms "estrobolome", "estrogen and gut microbiome", "phytoestrogen and gut microbiome", "phytoestrogens and cancer", "bariatric surgery and gut microbiome", "gut microbiome and epithelial function" and "physiology and estrogen or phytoestrogen". Further search terms included the disease states or aspects of health i.e. "cancer", "obesity",

* Corresponding author at: The University of Arizona College of Medicine-Phoenix, Building ABC-1, Office 330, Lab 331E, 425 North 5th St., Phoenix, AZ 85004-2157, USA.
E-mail address: mherbst1@email.arizona.edu (M.M. Herbst-Kralovetz).
[1] Present address: Department of Basic Medical Sciences, College of Medicine, University of Arizona, Phoenix, Arizona, USA.

http://dx.doi.org/10.1016/j.maturitas.2017.06.025
Received 2 June 2017; Received in revised form 20 June 2017; Accepted 22 June 2017

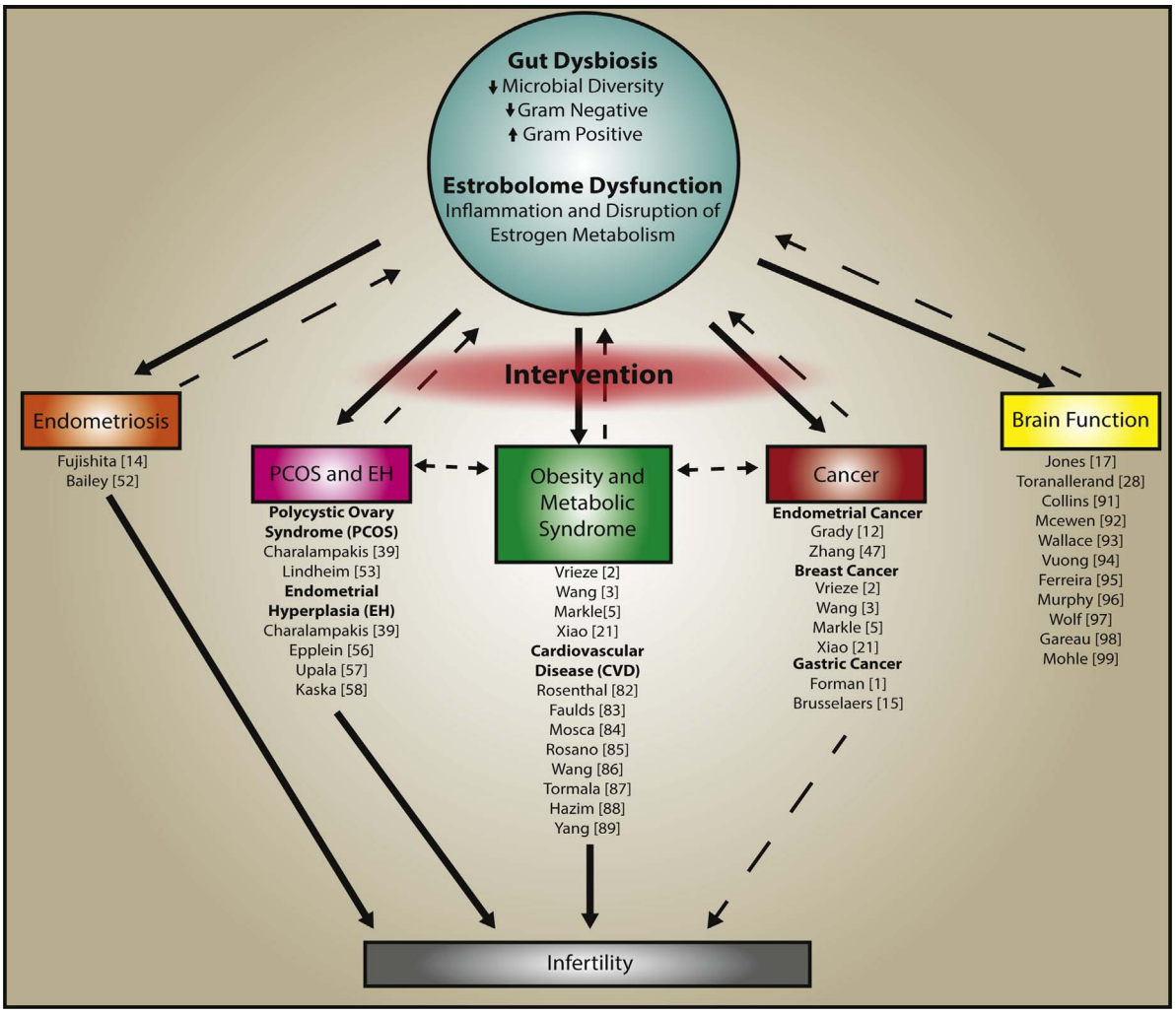

Fig. 1. Estrogen-gut microbiome interactions exhibit physiological and clinical implications. Dysbiosis and a reduction of gut microbiota diversity impacts the estrobolome, which may lead to a wide range of disease states, illustrated. Reduction in gut microbiome diversity as result of dysbiosis and inflammation reduces the β-glucuronidase activity. This reduced β-glucuronidase activity results in decreased deconjugation of estrogen and phytoestrogen into their circulating and active forms. The subsequent decrease in circulating estrogens alters estrogen receptor activations which may lead to the hypoestrogenic pathologies: obesity, metabolic syndrome, CVD and cognitive decline. Hyperestrogenic pathologies can also be driven by the estrobolome through the increased abundance of β-glucuronidase-producing bacteria, which leads to elevates levels of circulating estrogens to drive diseases such as endometriosis and cancer. Obesity/metabolic syndrome can impact other disease states such including PCOS, EH and ultimately fertility. Intervention: Bariatric surgery, metformin and FMT provide therapeutic interventions that can mitigate the associated disease state through modulation of the gut microbiota composition. Solid arrows indicate the established interaction between estrobolome and disease states; dashed arrows indicate putative feedback mechanisms or interactions.

"metabolic syndrome", "endometriosis", "endometrial hyperplasia", "polycystic ovary syndrome" "cardiovascular disease", "infertility" and "cognition" which were combined with the terms "estrogen" and "gut microbiome". Studies were manually examined and included for their relevance to the topic of this review. Pertinent original articles and reviews that were peer-reviewed, indexed in PubMed and written in English were included. The publication dates were not limited in order to fully review the literature available regarding gut microbiome and estrogen levels. The literature searches were performed between March 2017 and May 2017.

3. Gut microbiome and homeostasis

The gut epithelial barrier is maintained by a healthy, diverse gut microbiome composed primarily of 4 phyla: Bacteriodetes, Firmicutes, Actinobacteria and Proteobacteria. A balanced bacterial composition is key to maintaining intestinal immunity and homeostasis. A healthy gut microbiome consists of > 90% of species within the Bacteroidetes and Firmicutes phyla [18]. However, it is not only merely the combined abundance of Bacteroidetes and Firmicutes that have been associated with gut microbiome homeostasis. A lower Firmicutes/Bacteroidetes (F/B) ratio also correlates with health [18], for example, lean humans and mice have a significantly lower F/B ratio compared to their obese counterparts [18]. The metabolic profile also provides a key component of microbiota homeostasis in the gut microenvironment. Short chain fatty acids (SCFAs) such as butyrate provide a well-defined example of how the metabolites produced by a healthy microbiome confer with epithelial barrier integrity and immunological homeostasis (Fig. 2) [19]. Butyrate provides an energy source for colonic epithelial cells and exhibits immunmodulatory and anti-inflammatory properties that contribute to the maintenance of epithelial barrier integrity [20]. Gut microbiome diversity is important since a more diverse gut microbiome contains a greater diversity and abundance of enzymes capable of synthesizing metabolites such as butyrate that then contribute to gut homeostasis and health [21].

An imbalance of the gut microbiota is referred to as dysbiosis and has pathophysiological consequences. Dysbiosis disrupts homeostasis through a reduction of bacterial diversity and an increased F/B ratio that leads to an inflammatory response and metabolic profile that is detrimental to gut epithelial health [18]. Gut epithelial barrier integrity has been shown to be influenced by dysbiosis through the reduction in cell–cell junctions leading to increased permeability and subsequently