Review

MOLECULAR METABOLISM

Sexual dimorphism of cardiometabolic dysfunction: Gut microbiome in the play?

Tzu-Wen L. Cross [1,2,*], Kazuyuki Kasahara [2], Federico E. Rey [1,2]

ABSTRACT

Background: Sex is one of the most powerful modifiers of disease development. Clear sexual dimorphism exists in cardiometabolic health susceptibility, likely due to differences in sex steroid hormones. Changes in the gut microbiome have been linked with the development of obesity, type 2 diabetes, and atherosclerosis; however, the impact of microbes in sex-biased cardiometabolic disorders remains unclear. The gut microbiome is critical for maintaining a normal estrous cycle, testosterone levels, and reproductive function. Gut microbes modulate the enterohepatic recirculation of estrogens and androgens, affecting local and systemic levels of sex steroid hormones. Gut bacteria can also generate androgens from glucocorticoids.

Scope of review: This review summarizes current knowledge of the complex interplay between sexual dimorphism in cardiometabolic disease and the gut microbiome.

Major conclusions: Emerging evidence suggests the role of gut microbiome as a modifier of disease susceptibility due to sex; however, the impact on cardiometabolic disease in this complex interplay is lacking. Elucidating the role of gut microbiome on sex-biased susceptibility in cardiometabolic disease is of high relevance to public health given its high prevalence and significant financial burden of related disease.

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Keywords Sex differences; Steroids; Gut microbiota; Metabolic disease; Cardiovascular disease

1. INTRODUCTION

Humans harbor over 100 trillion microbes, with the gastrointestinal tract being the most densely populated body habitat [1,2]. Gut microbial communities include members of the Bacteria, Archaea, and Eukarya (fungi, protozoa) domains, as well as viruses. Their collective genomes encode for metabolic pathways essential for acquiring nutrients that are indigestible to us and for the generation of metabolites that modulate our metabolism. While some of the effects of gut microbes on the immune system and gut physiology have been recognized for a long time, over the last decade, we have developed a deeper appreciation for the many roles these organisms play in virtually every aspect of our biology.

Although there is substantial interpersonal variation in the composition of the distal gut microbiota among unrelated, healthy subjects, sequence-based studies have revealed distal gut community patterns associated with different pathological states, including metabolic syndrome. Remarkably, recent studies indicate that the gut microbiota influences the development of cardiometabolic disease:

- Sub-therapeutic antibiotic therapy in young, conventionally-raised mice results in taxonomic changes in the distal gut microbiota and increases adiposity [3].
- Mice of the same genotype, but with different microbiota composition, develop different metabolic phenotypes in response to chronic high-fat/high-sucrose feeding [4].
- Germ-free mice are resistant to diet-induced metabolic disease [5].
- The absence of the gut microbiome differentially impacts the atherosclerosis susceptibility of apolipoprotein $E^{-/-}$ ($ApoE^{-/-}$) mice compared to conventionally-raised mice (i.e. fully colonized with microorganisms at birth) [6].
- Transplantation of gut microbiota from genetically obese mice or obese humans, to lean, germ-free mice transfers an increased adiposity phenotype [7].
- Transfer of gut microbiota from lean, metabolically healthy human donors to humans with metabolic syndrome increases their insulin sensitivity, and this improvement is linked to changes in plasma metabolites [8]. However, beneficial effects are transient, and response is driven by baseline fecal microbiota composition [9].

[1]Cardiovascular Research Center, University of Wisconsin-Madison, Madison, WI, 53705, United States [2]Department of Bacteriology, University of Wisconsin-Madison, Madison, WI, 53706, United States

*Corresponding author. University of Wisconsin-Madison, 5157 Microbial Sciences Building, 1550 Linden Drive, Madison, WI, 53706, United States.

E-mails: tlcross@wisc.edu (T.-W.L. Cross), kasahara2@wisc.edu (K. Kasahara), ferey@wisc.edu (F.E. Rey).

Abbreviations: ApoE, apolipoprotein E; BAs, bile acids; CVD, cardiovascular diseases; E1, estrone; E2, estradiol; E3, estriol; ER, estrogen receptor; FCG, four core genotypes; FMO3, flavin monooxygenases 3; FXR, farnesoid X receptor; GI, gastrointestinal; GPR30, G protein-coupled receptor 30; HDL-c, high-density lipoprotein cholesterol; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LDL-c, low-density lipoprotein cholesterol; LPS, lipopolysaccharides; MUC2, mucin-2; NOD, non-obese diabetic; SHP, small heterodimer partner; T1D, type 1 diabetes; T2D, type 2 diabetes; TLR4, Toll-like receptor 4; TMA, trimethylamine; TUDCA, tauroursodeoxycholic acid; ZO-1, zonula occludens

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Review

This evidence highlights the importance of the gut microbiome on the etiology of cardiometabolic disease. Additionally, clear sexual dimorphism exists in cardiometabolic disease. Cardiovascular diseases (CVD) are more common in men than age-matched premenopausal women. However, this cardioprotection in women is lost once menopause occurs, suggesting the contribution of sex steroid hormones on varying disease susceptibility. Globally, more men are diagnosed with type 2 diabetes (T2D) than women [10]. Men tend to be overweight at a younger age, whereas women tend to be overweight or obese after the age of 45 [11]. Similarly, male mice develop diet-induced obesity and insulin resistance more rapidly than females [12,13]. Furthermore, obese female mice are more protected against inflammation and glucose intolerance relative to age- and weight-matched males, indicating that the protective effect of estrogen persists in the obese state [12]. Sex steroid hormones also modulate gastrointestinal (GI) health [14,15]. Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are more prevalent in women than in men. These GI disorders have been associated with greater gut permeability due to compromised gut barrier function, which can result in increased levels of pro-inflammatory molecules entering into systemic circulation. Moreover, the symptoms of IBD fluctuate across the menstrual cycle in humans [16] and the mucosal infiltration of immunocytes (i.e., immunologically competent cells) in IBS patients differs between females and males [17]. Data from experimental models show that female rats are more resistant to intestinal injury and inflammation than males [18]. In females, GI permeability fluctuates throughout the estrous cycle, and ovariectomy-induced estrogen deficiency leads to compromised barrier function [19,20]. This evidence supports that, besides the role in reproductive functions, sex steroid hormones play important roles in GI homeostasis and modulate the susceptibility of diseases, fundamentally contributing to sexual dimorphism (Figure 1).

2. SEXUAL DIMORPHISM IN STEROLBIOME

Sex steroid hormones and bile acids (BAs) share structural similarity as they are both derivatives of cholesterol which contains cyclic steroid nucleus. They can both be recycled through enterohepatic circulation—a process, in part, regulated by the gut microbiome. Therefore, the action of gut microbes on these steroids is critical in determining whether they are excreted or recycled. Various microbial modifications also alter the cytotoxicity and/or potency of these steroids. The term "sterolbiome" has been recently proposed to describe the genetic potential of the gut microbiome to produce endocrine molecules from endogenous and exogenous steroids [21]. Below, we discuss the current knowledge on the sterolbiome and its impact on sexual dimorphism and cardiometabolic disease.

2.1. Bile acids

Traditionally viewed as surfactants, BAs facilitate the absorption of lipids and fat-soluble vitamins, have antimicrobial effects, and play important signaling roles modulating glucose homeostasis, lipid metabolism, energy expenditure, and intestinal motility. Primary BAs are synthesized in the liver from cholesterol and stored in the gallbladder. Upon consumptions of food, primary BA conjugates of taurine (most mammals) and glycine (humans) are secreted into the duodenum, with a large fraction then reabsorbed in the ileum. BAs that escape reabsorption modulate the composition of the gut microbial community at least in part by inhibiting growth of specific microbes [22,23], and are subjected to microbial modification which generate secondary BAs via deconjugation, dehydrogenation, epimerization, and dehydroxylation of primary BAs. BAs with different modifications vary in their ability to activate receptors, act as antimicrobial agents, and impact host physiology. Changes in the homeostasis of BA have been associated with alterations in metabolic health: (i) a bacterial enzyme

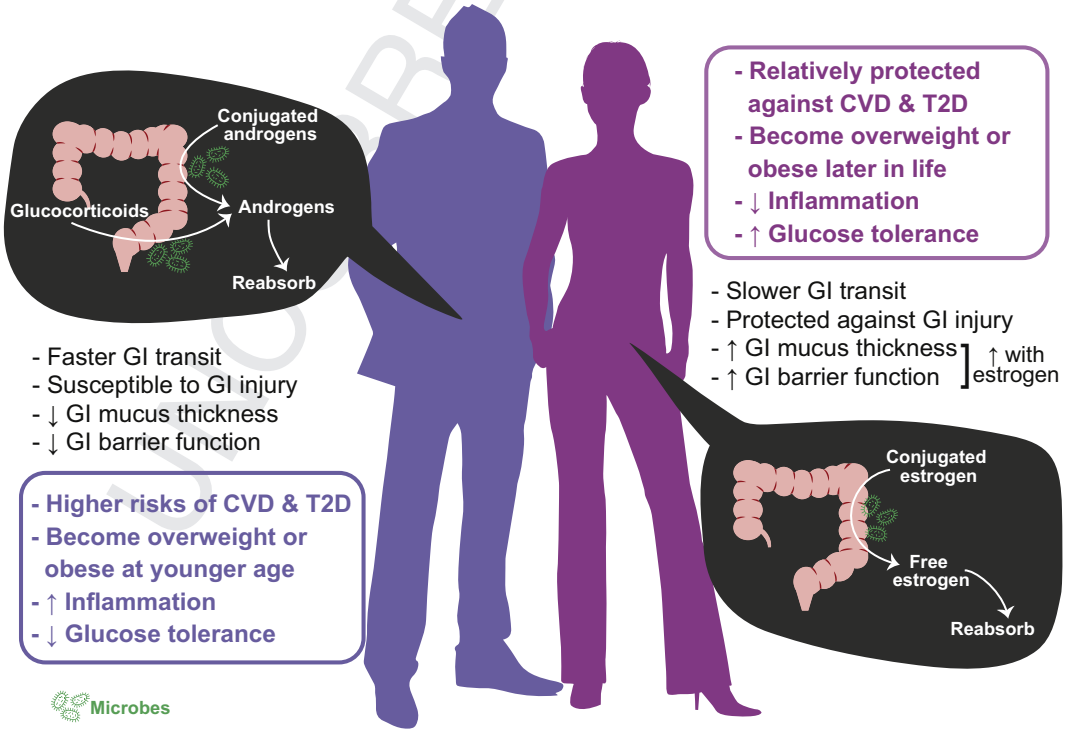

Figure 1: Sex differences in cardiometabolic disease and the gut microbiome. GI: gastrointestinal; CVD: cardiovascular disease; T2D: type 2 diabetes.

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