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Polycystic Ovarian Syndrome Managed by Faecal Transplant Therapy

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Abstract

The exact cause of polycystic ovarian syndrome (PCOS) is unknown; most likely genetics, obesity, higher levels of androgens may play a role. High androgen levels prevent ovaries from releasing eggs, which causes irregular menstrual cycles and infertility. Women with PCOS are more likely to develop certain serious health problems. These include type 2 diabetes, high blood pressure problems with the heart and blood vessels, and uterine cancer. PCOS cannot be cured but can be managed by symptomatic treatments. Recent studies on Faecal Transplant Therapy proved that PCOS were managed very well. A new hypothesis is being proposed to use FMT and curcumin combination as an effective and sustained treatment of PCOS with much lower rates of remission.

Keywords: Androgens, Microbiota, Estrobolome, Symptomatic Treatments, Curcumin.

Introduction

Polycystic ovary syndrome (PCOS) is a result of imbalance of hormonal milieu. Subjects with PCOS often have irregular menstrual cycles, missed periods and unpredictable ovulation due to the high levels of ovarian hormones. In an anovulatory cycle, small follicle cysts may be visible on the ovaries on ultrasound examination [1, 2]. PCOS is characterized by the presence of three main features: hyperandrogenism, oligo/anovulation, and polycystic ovaries on pelvic ultrasound [3]. The etiology and pathogenesis of PCOS remain still unclear and may be multi-factorial, involving genetic, neuroendocrine, and metabolic causes. However, it is not essential to have cysts on the ovaries to have PCOS, more so even if they are present they are not dangerous or painful. Combination of various symptoms like hirsutism, chronic amenorrhea, infertility, obesity, polycystic ovaries, acne, darkening of the skin, cysts, thinning hair, presence of skin tags, etc are characteristics of PCOS. It is surprising to note that there exists a strong relationship between the microbiota of the gut and female reproductive tract.

The Mighty Microbiota: Regulator of the Human Body

An alteration in the intestinal microbial community plays a major role in human health and diseases such as PCOS. These alterations in microbiota may be due to change in lifestyle and/or the presence of an underlying disease and the dysbiosis increases host susceptibility to infection [4]. Specific metabolic activities and functions of these micro-organisms depend on the unique diversity of the human microbiota. Previous studies have estimated that there are 10 times as many bacteria in our bodies than human cells, though Prof. Milo and colleagues revised this number to be around 38 trillion [4-6].

Similar to the gut, the female reproductive tract is an example of a very complex biological ecosystem. Recent studies correlated a possible association between the gut and female reproductive tract microbiota [7, 8]. About 5–10% of women in their reproductive years suffer with PCOS. The GI gastrointestinal microbiota plays a potentially significant but enigmatic contribution to human health via the estrobolome, the aggregate of the enteric bacteria and/or bacterial genes whose products are capable of metabolizing estrogens to keep the estrogen in check. It has been suggested that a woman's estrobolome also plays a key role in a number of hormonal disorders, including breast, endometrial, and ovarian cancers [9, 10].

Lindheim et al. (2017), compared stool microbiome of women with PCOS and healthy controls. The stool microbiome of PCOS patients showed a lower diversity and an altered phylogenetic composition compared to controls. Significant differences in taxa, with a relative abundance >1%, were not observed [3].

Gut Microbiota of Subjects Suffering with PCOD

The female reproductive tract has developed unique structures, such as the vagina and uterus. While the vagina hosts trillions of bacteria, the upper reproductive tract remains largely unexplored though generally been considered sterile. Vaginal microbiota is a complex ecosystem of more than 200 bacterial species

influenced by genes, ethnic background and environmental and behavioural factors [11]. It is interesting to find that the vaginal microbiota interacts with the immune system. The relationship between the gut and female reproductive tract microbiota has been studied in-depth [12].

Microbiota of individuals with PCO harboured a markedly elevated number of Bacteroides vulgatus in the gut supporting the idea that changes in the gut microbiome may play a causal role in this disorder. A potentially ground-breaking study also gave a clue that transplantation of a dysbiotic gut microbiome from women with PCOS or Bacteroides vulgatus is sufficient to induce a PCOS-like phenotype in mice [13].

Alpha as well as beta diversity of gut microbiota is altered in women with PCOS compared with healthy women. Of the genera within phylum Bacteroidetes, Bacteroides were positively associated with PCOS in 5/7 studies and Parabacteroides were positively associated with PCOS in 2 studies, while the family S24-7 was negatively associated with PCOS in 2 studies [14-18]. Of the genera within phylum Firmicutes, family Clostridiaceae was positively associated with PCOS in 2 studies and family Veillonellaceae in 2 other studies [16, 18, 20]. Of the genera within phylum Proteobacteria, Escherichia, and Shigella were positively associated with PCOS in 2 studies [8, 14, 19].

Dysbiosis of the Intestinal Microbiota and PCOS

Recently, a potential relationship between sex hormones and gut microbiota emerged since, PCO has a link with imbalance of the sex hormones. This novel concept has been defined as "microgenderome" [21].

Tremellen and Pearce suggested the idea that dysbiosis of the gut microbiota (DOGMA) is a causative factor of metabolic and reproductive manifestations of PCOS due to a high fat-sugar diet in PCOS patients leads to an increase in intestinal permeability (Fig-1) [22]. Lipopolysaccharide produced by Gram-negative bacteria traverse the gut wall to enter the circulation, leading to a chronic state of low-grade inflammation. The immune system gets activated thereby interfering with insulin receptor, driving up insulin levels, boosting testosterone production in the ovary, leading to PCOS. DOGMA theory may account for the role of gut microbiota in the pathogenesis of PCOS [22]. Studies where both women with PCOS and rodent models of PCOS demonstrated that hyperandrogenism is associated with gut microbial dysbiosis, indicating that androgens may modulate the gut microbial community in females. An interesting observation is that in one study the faecal microbiome transplantation of stool from women with PCOS or exposure to certain bacteria resulted in a PCOS-like phenotype in mice, while other studies showed that exposure to a healthy gut microbiome, pre/probiotics, or specific gut metabolites resulted in protection from developing PCOS-like traits in mice. Altogether, it is clear that these results suggest a dysbiosis of the gut microbiome may be sufficient to develop PCOS-like symptoms and so modulation of the gut microbiome may be a potential therapeutic target for PCOS [22].

Potential mechanisms through which testosterone could alter the gut microbiome include a direct effect as a substrate for gut microbial enzymes and an indirect effect via activation of host androgen receptors or modulation of the immune system (reviewed previously) [23, 24].

Both alpha diversity and beta diversity were associated with hyperandrogenism (HA), indicating that higher testosterone levels are linked with changes in the overall composition of the gut microbial community as mentioned earlier. Within the phylum Actinobacteria, the genus Collins Ella was positively correlated with testosterone levels in 2 studies. Within the phylum Bacteroidetes, the genus Bacteroides was positively correlated with testosterone levels in 4 studies. Furthermore, the genus Prevotella was negatively correlated with the levels of testosterone in 1 study and positively correlated with testosterone in 3 studies. Within the phylum Proteobacteria, Enterobacteriaceae were positively correlated with testosterone. Bifidobacteriaceae was negatively correlated with testosterone while Bacteroides, Streptococcus, and Prevotella were positively correlated with testosterone, consistent with the human studies. Overall, these studies show promise that adjusting the gut microbial community in women with PCOS may decrease some of the diet-independent, hyperandrogenic-induced symptoms. Regarding rare taxa, the relative abundance of bacteria from the phylum Tenericutes (relevant genera include Mycoplasma spp., Ureaplasma spp.) and the family S24-7 (phylum Bacteroidetes) was significantly lower. Moreover, patients did not show alterations in all markers of gut barrier function and endotoxaemia. These findings suggest that changes of gut microbiota also had trends similar to the variations of metabolic symptoms. Other studies observed that some Gram-negative bacteria belonging to the genera Bacteroides and Escherichia/Shigella significantly increased in the gut of PCOS women with obesity [25].

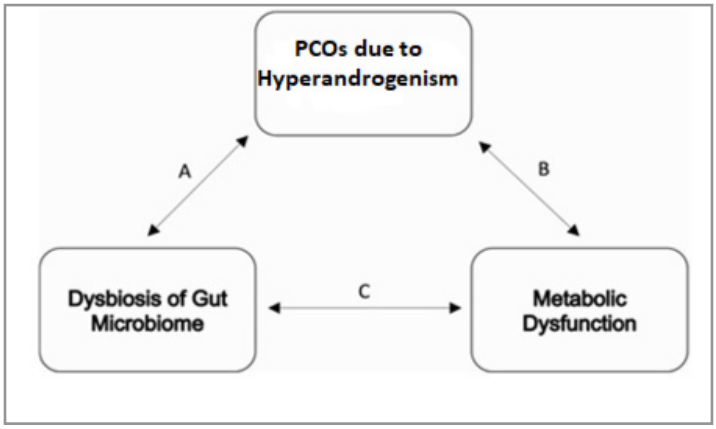

Figure 1: Correlations between hyperandrogenism, dysbiosis of the gut microbiome, and metabolic dysfunction

A: Link between HA and dysbiosis of the gut microbiome. Recent studies in women and rodent models demonstrated that HA is correlated with dysbiosis of the gut microbiome, including changes in the overall biodiversity of gut bacteria as well as the relative abundance of certain bacteria. In addition, recent study reported that introducing stool from women with PCOS or a bacterial species (B. vulgatus) in antibiotic-treated mice resulted in HA, suggesting that gut microbial dysbiosis or the overabundance of specific bacteria may be sufficient to induce PCOS-like symptoms.

B: Link between HA and metabolic dysfunction. Metabolic dysfunction, including weight gain, insulin resistance (IR), and dyslipidemia, occurs predominantly in women with PCOS diagnosed with HA and ovulatory dysfunction, independent of body mass index.

C: Link between dysbiosis of the gut microbiome and metabolic dysfunction. Gut dysbiosis has been associated with obesity, IR, and impaired lipid metabolism in metabolic diseases, including metabolic syndrome, type 2 diabetes, nonalcoholic fatty liver disease, and PCOS. Despite the tripartite set of correlations between HA, gut microbial dysbiosis, and metabolic dysfunction, the mechanisms of how each player affects the other 2 are still largely unknown.

Faecal Microbiota Transplants as a Therapeutic Agent for PCO

As dysbiosis is considered as one of the prime underlying causes of PCOS, restoration of eubiosis was considered as a plausible way to treat it [26]. Understanding the connection between intestinal and vaginal microbiota is indispensable for new treatments in female genital tract disorders. The cross talk between the bacterial strains resident in the gut and vagina may result in local and systemic immune regulation is worth focussing our attention during treatment. Induction of humoral and cellular immune responses represents a fundamental aspect involved in preventing female genital tract disorders. As other secretions, vaginal and cervical fluid contains mainly IgA and a certain proportion of IgG of plasma origin. Organized lymphoepithelial structures analogous to intestinal Peyer's patches are missing in the female genital tract. This aspect is crucial to identify alternative routes of immunization to bypass local application of antigens and so oral, rectal and nasal administrations were suggested. Bacteriotherapeutic like probiotics, symbiotic and even faecal microbiota transplant (FMT) have shown considerable effectiveness in PCOS [27]. Of these bacteriotherapeutic options, FMT is considered to be the most holistic as it encompasses the bacteriome, virome, fungome, archaeome and even parasitome while both robotics as well as synbiotics mainly comprise bacteria. In depth study on the intricate relationships between the gut virome, mycobiome, bacteriome, and host immunity underlying FMT effectiveness, beneficial effects and health concerns, highlights on the roles of bacteriophages and Candida species in FMT efficacy was in vogue in the recent past [28].

Certain microbes are capable of consuming polyphenols as substrates and its positive effect on bacterial consumption of nutrients such as sugars. A new hypothesis is being proposed to use FMT and curcumin combination as an effective and sustained treatment of PCOS with much lower rates of remission [29]. Two aspects clearly emerged from the study [11] are

(1) the administration of live bacterial vectors induces a local and systemic immune response;
(2) rectal administration may also induce stimulation at the cervicovaginal level. In this regard, FMT could be a natural alternative to recombinant bacterial vectors.

In fact, with single or multiple infusions, large amounts of bacteria and metabolites could be administered, each of which could serve as an inducer of local and systemic immune responses [11].

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