

The Important Role of Bowel Habit in Polycystic Ovary Syndrome (PCOS): Evidence from Persian Medicine to Modern Medicine

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Received date: March 02, 2022, Manuscript No. IPMCR-22-12391; **Editor assigned date:** March 04, 2022, PreQC No. IPMCR-22-12391 (PQ); **Reviewed date:** March 18, 2022, QC No. IPMCR-22-12391; **Revised date:** March 23, 2022, Manuscript No. IPMCR-22-12391 (R); **Published date:** March 30, 2022, DOI: 10.36648/2471-299X.8.3.187

Citation: Tabarraï M (2022) The Important Role of Bowel Habit in Polycystic Ovary Syndrome (PCOS): Evidence from Persian Medicine to Modern Medicine. Med Clin Rev Vol.8 No.3: 187

Description

Polycystic ovary syndrome (PCOS) is a complex disorder with negative metabolic and reproductive consequences that has no definitive treatment due to poorly understood etiology and pathophysiology. All studies and guidelines emphasize that lifestyle modification is the first line of treatment in this syndrome. A healthy lifestyle in Persian medicine is based on six important principles. Regular excretion and prevention of constipation is one of these. Constipation is common in PCOS and also is one of the major causes of disturbances in Intestinal bacterial flora (Gut Microbiota dysbiosis). Intestinal flora plays critical role in maintaining good health. Its imbalance is effective in the pathogenesis of metabolic diseases. Recent studies have reported that PCOS women have change in Gut Microbiota composition. Therefore, it is hypothesized that GM dysbiosis may play a role in PCOS development as a spectrum of metabolic syndrome, although its specific mechanisms remains unclear. So Prevention of constipation is very important in the lifestyle of PCOS women. but fewer studies have addressed this issue.

the present study aims to investigate the articles related to role of constipation on PCOS pathogenesis and the importance of its prevention according to the principles of healthy lifestyle in Persian medicine and modern medicine. data bases are searched from 2014 to 2020 with a number of related keywords. Articles are classified based on the correlation between constipation and PCOS risk factors. Finally, 104 articles are selected in this regard.

It seems that attention to the prevention of constipation is important according to the available scientific evidence and the theory of Persian medicine regarding the correlation between normal bowel habit and maintaining good health in all people, including PCOS women. Of course, clinical trials in the future can better confirm this hypothesis.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common

endocrine and metabolic disorders in reproductive age women, with a prevalence of %5 to 18% and uncertain underlying exact etiology and pathophysiology. PCOS is characterized by hyperandrogenism, insulin resistance, chronic anovulation, and polycystic ovary morphology. Extensive health problems of PCOS in reproductive and menopause periods are a set of negative metabolic outcomes, such as central obesity, type2 diabetes, cardiovascular disease, reproductive problems (including menstrual disorders, sterility), and psychological disorders. These can reduce life quality and expectancy of PCOS women and increase their risk of death in the long run.

Early distinction, treatment and subsequent preventions of the syndrome can reduce the risk of these consequences. Lack of effective cure for PCOS, due to the unclear mechanism, significant interpersonal differences in the occurrence of symptoms, and lack of evaluation of symptoms as a single set that leads to delay (at least 2 years) in early diagnosis of the disease in 30% of PCOS women, are the major problems in its management. So, most treatments have been symptomatic and based on patients' complaints Which are associated with many complications.

Multiple factors such as genetic or lifestyle causing PCOS, in which lifestyle mistakes seems to be the main cause. Despite the variety of pharmacological, hormonal, and surgical treatments, none of them can reduce the symptoms and consequences of the disease as much as lifestyle correction can. So more effective strategies for lifestyle modification must be used to be successful in PCOS management

Persian Medicine (PM), as one of the oldest rich medical school with a holistic view to human health, suggests a different viewpoint to chronic diseases. In this view, drug therapy is not the first step in management of disease PM scholars believes in modifying the lifestyle and considers the observation of 6 health principles (known as Asbab-e-Setteh-e-Zarurieh) for the prevention and treatment of all diseases One of the six pillars of maintaining good health is the principle of retention and release (Ehtebas and Estefragh) , including the regulation of waste disposal, such as constipation prevention and treatment.

Iranian Traditional Medicine

Chronic constipation is one of the most common gastrointestinal tract (GIT) disorders. With a worldwide prevalence of 15% that is more common in women than in men based on a meta-analysis. Today, constipation is raised as one of the most important causes of Gut Microbiota dysbiosis.

In recent years, numerous studies have shown a change in the gut microbiota composition and reduced microbial diversity of PCOS patients. Furthermore, Modulation of the microbiome itself, is a new potential therapy for PCOS women. Therefore, it is hypothesized that Gut Microbiota dysbiosis is likely to play a role in PCOS pathogenesis. Attention to the maintenance and improvement of gut microbiome through the prevention and treatment of constipation can be considered as an effective approach and cost-effective treatment.

In the reviewed articles, researchers have mainly focused on dietary change, physical activity, behavioral therapy, and weight loss for lifestyle modification in PCOS. In this regard, there has been no article focusing on constipation management in this syndrome. This study provides an overview of research related to the correlation of constipation and PCOS according to the perspective of Persian medicine and growing evidence.

Research Methodology

In this review study, the sources of PM and modern medicine were examined using the keywords of "PCOS", "Polycystic ovary syndrome", "constipation", "Gut Microbiota", "dysbiosis", "Gut Microbiome", and "Lifestyle" were searched in medical information databases of Scopus, pub med and Web of science. The search was limited to the English articles between 2014 and 2020. The titles and abstracts of all the articles were controlled, and finally, out of 157 articles related to the subject that were in English and with full text, 104 articles were selected for discussion in 6 axes. Also, titles and contents related to digestive problems in PCOS in the valid sources of PM, including al-Qanun fi al-tibb (Canon of Medicine), Kholase al hekmah, Zakhire Kharazmshahi, and Exir Azam, were discussed by authors.

Chronic functional constipation with a prevalence of about 24%, is one of the most common GIT disorders, which is defined by ROMEIII criteria by excessive forcing during defecation, hard and fragmented defecation, dry stools, feeling of incomplete defecation, defecations less than 3 times a week, and feeling of anorectal blockage. A normal bowel habit is the result of complex interaction of the intestinal, autonomic and central nervous systems with immune system, bile metabolism, mucous secretions, the internal environment of the intestinal lumen, and also the intestinal microbiota. Its etiology and pathophysiology are uncertain. Genetics and lifestyle seem to influence the pathogenesis of constipation. Various factors, such as bad bowel habits of postponing, lack of regular physical activity and exercise, as well as high-fat food, and very intense and long-term exercise and physical activity can cause constipation with the release of stress hormones, composition changes of intestinal flora, and impairment of bowel nerve function. It is known that constipation is associated with an increased risk of serious

diseases, both inside and outside the intestine. Therefore, it is very necessary to pay attention to its prevention and treatment.

Constipation and PCOS

Studies have shown that women are 2-3 times more likely than men to develop chronic idiopathic constipation, which can impair their life quality and increase the risk of cardiovascular disease, stroke, and colorectal cancer. Irritable Bowel Syndrome (IBS), with its predominance of constipation, is a common gut disorder in women with PCOS, the cause of which is unknown. Both IBS and PCOS seem to be the result of a common causative factor. In 1909, Arbuthnot Lane's astute described a type of chronic intestinal stasis that was almost limited to women under 35 years. Peripheral vascular disease, bloating, amenorrhea, sterility, lack of secondary sexual characteristics, and ovarian cysts were more common in these patients.

Later on, Preston and Lennard Jones (1986) as well as Waldron et al. (1988) each described women with severe chronic constipation, who had extensive gut, gynecological, urinary problems, and a widespread autonomic disorder in the form of cold hands or epilepsy that led to a disability and impairment in the social and occupational performance. Preston and Lennard Jones hypothesized that a disorder in the secretion of sex hormones may affect the gut or, conversely, the enterohepatic circulation of estrogen may be affected by disorders in the gut. The gynecologic statuses, such as menstrual disorders, vaginal secretion, sterility, and PCOS occur more often in women with IBS compared to the general population.

Chronic Constipation and Gut Microbiota Dysbiosis

Increasing evidence suggests that there is an association between constipation and gut microbiota and there is a significant difference in gut microbial compositions of constipated patient compared with healthy individual. In a study by Ge et al., transplantation of constipated mouse intestinal microbiota in healthy mice showed GM composition change and symptoms of constipation. Bacteria affect gastrointestinal motility through their metabolites. For example, the gut flora can ferment cellulose into short-chain fatty acids (SCFAs), which can cause intestinal peristalsis release through 5-HT release. Some studies have established that the gut microbiota dysbiosis can affect SCFA production, which can further decrease production of glucagon peptide-1 (glp-1), and inhibit function of intestinal transmission. GM dysbiosis can affect intestinal motility, immunity, gastrointestinal secretory and barriers functions by altering the metabolic environment of the gut and disrupting GM-gut-Brain axis signals, playing a key role in the pathophysiology of functional constipation. On the other hand, the prolonged stopping of stool in the intestine of patients with chronic constipation can change the composition and number of intestinal microbiota by worsening the intestinal environment conditions. Chronic constipation is associated with a relative decrease of good bacteria (such as Lactobacillus, Bifidobacterium, and Bacteroides spp.) and an increase in strongly pathogenic intestinal microorganisms (such as

Pseudomonas aeruginosa and *Campylobacter jejuni*) compared to the control group. Although the causal relationship between constipation and GM dysbiosis is not fully elucidated and there is still no consensus on this issue, evidence suggests that intestinal microbiome and intestinal physiology interact with each other.

Insulin Resistance (IR) and GM Dysbiosis

In 2012, the hypothesis of " Gut Microbiota dysbiosis " was proposed by Tremellen and Pearce in justifying two major conditions of Insulin resistance (IR) and inflammation in PCOS. They argued that altered intestinal microbes could interfere with the activated immunity of the body with increased insulin level by increasing intestinal mucosal permeability and the entry of lipopolysaccharides related to the gram-negative intestinal bacteria into the systemic circulation. This, in turn, can increase ovarian androgen production in the ovaries and then, disrupt the growth and normal function of follicles by causing a chronic inflammatory reactions and IR. It is estimated that 50-70% of women with PCOS have varying severity of IR, which caused by various internal and external factors including GM dysbiosis, food, physical activity, stress, environment, and even intrauterine conditions and birth weight. Regardless of BMI and patient weight, IR plays a key role in the PCOS pathophysiology and increase the severity of metabolic syndrome in this syndrome. In a human study by Vrieze et al., fecal transplantation from a healthy thin donor reduced IR in patients with metabolic syndrome. Studies in mice have shown that intestinal bacteria are able to increase IR by disrupting the intestinal epithelial barrier and the entry of bacterial endotoxin into the systemic circulatory system. Guo et al suggested, Fecal microbiota transplant from PCOS rat to healthy female rat changes ovarian morphology and estrogen level, due to the high relation of GM dysbiosis with host sex hormone level. A human study by Liu et al. showed association between GM dysbiosis and clinical manifestations of PCOS, such as inflammation, obesity, insulin resistance, increased androgen, abnormal ghrelin, and mental state. Changes in the intestinal microbial community through the insulin-testosterone axis are likely to play a role in PCOS pathogenesis.

Intestinal Permeability and GM dysbiosis

Increasing research suggests that there is an important link between the gut health and overall body health. The human body has numerous epithelial barriers that protect the host's internal environment from the influence of external factors. The gut is one of the largest of these barriers, which plays an important role in regulating the immune system and the health of the whole body. In ideal conditions, the epithelial lining of the intestine provides the possibility of absorbing nutrients and also prevents the passage of potentially harmful antigens and microorganisms from the gut to the blood and surrounding tissues by creating a strong barrier. The outer mucosal layer of the colon allows colonization of symbiotic bacteria (which play a vital role in the colon). These bacteria are the second line of

defense for the intestinal barrier, which prevents pathogenic bacteria from invading by occupying the connection points. Trillions of microorganisms living in various parts of the human gut, especially the colon, have a peaceful coexistence with their hosts. In recent years, the vital role of GM in the health and pathogenesis of many metabolic diseases and nervous systems has received much attention from researchers. All aspects of human health throughout life are affected by GMs. GMs are effective in preventing and treating any decline in the brain function during old age by affecting the health and development of the immune system in infancy and protecting the function of the intestinal barrier in aging. Today, coexistent GMs in the intestine regulate many physiological functions of the body by producing the most important metabolites, including SCFA, contains butyrate, propionate, and acetate, that affect brain-bowel signals, immune system modification, inhibiting the invasion of pathogens, helping the digestion system, releasing nutrients from the food received, and improving the function and development of the host intestine. Also, normal GM plays a very important role in normal intestinal motility. Strong and growing evidence suggests that the GM-gut -Brain axis plays a key role in regulating intestinal motility. Functional impairment at any level of this axis can cause intestinal motility disorder. Bacterial metabolites or its cellular components interact with the intestinal hormonal nervous system (ENS) and affect the intestinal transit by regulating the stimulatory effect of the serotonin (5 HT). SCFA also can directly stimulate the contraction of the smooth muscles of colon and ileum 5-hydroxytryptamine (5 HT) is a key neurotransmitter in the brain-bowel axis that plays an important role in the intestinal motility. In the physiological state, serotonin transmitter (SERT) help regulate and balance gut motility by reabsorbing additional 5HT from affected areas and terminating the physiological effects of 5HT. In the normal state, SERT expression in the epithelial cells of the intestinal mucosa is regulated by intestinal microbes. Improper nutrition, stress, obesity, antibiotics and prolonged stasis of stool in the intestines of patients with constipation lead to altered intestinal microbiomes. GM dysbiosis reduces bowel peristaltic movements by affecting excessive expression of SERT and excessive reabsorption of 5HT and also destroys the intestinal mucosal barrier by disrupting the intestinal mucin production and causing dry stools. Damage to the mucosal structure and loss of intestinal barrier strength increase the intestinal permeability (IP), leakage of toxins, microorganisms, and undigested food from the intestinal wall into the portal vein, which is associated with increased serum levels of endotoxins and local and systemic immune response of body and increased production of inflammatory cytokines. Research shows that there is a strong connection between the intestine and the brain. Therefore, any condition that impairs the bowel function, can lead to the brain and body physiology dysfunction. The association of IP with a wide range of gut, hepatic, autoimmune, diabetes, autism, and allergic diseases, particularly PCOS and IBS, has been proved as an influential factor in their pathophysiology. The severity of PCOS is also directly related to IP with the clinical manifestation of menstrual disorders.