

AN OVERVIEW ON INTESTINAL PARASITES AND GUT MICROBIOME: A BIDIRECTIONAL RELATIONSHIP

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Abstract

The human body hosts a vast and diverse ecosystem known as the microbiota, inclusive of bacteria, viruses, archaea, and parasites. The majority of gut microbiota resides in the colon, with *Firmicutes* and *Bacteroidetes* representing the predominant phyla. Disruption of gut microbiota (dysbiosis) is associated with various intestinal and systemic diseases. Development of intestinal parasitic infections may alter bacterial composition, immune responses, and homeostatic relationships within the gut ecosystem. Protozoa, like *Giardia intestinalis*, *Entamoeba histolytica*, and *Blastocystis* cause interactions with resident bacteria, impacting the microbiota's composition and diversity. *Toxoplasma gondii* influences gut microbiota leading to changes in bacterial load, diversity and translocation. Owing to their immunomodulatory effects, helminths as *Trichuriasis* exhibit potential control of autoimmune diseases. The relationship between the gut microbiome and intestinal parasites is intricate and dynamic. The microbiome can influence parasitic infections, affecting immune responses and disease outcomes.

Keywords: Gut microbiota, Intestinal parasites, Dysbiosis, An overview.

Introduction

Generally, human microbiota consists of 10-100 trillion symbiotic microbial cells harboured by each person, mainly bacteria in the gut; the microbiome consists of these cells genes (Turnbaugh *et al*, 2007). Globally, microbiome projects were launched to know the roles these symbioses play on human health (Dave *et al*, 2012). Human microbiota composed of bacteria, viruses, parasites, and archaeans most of them inhabit the GIT (Rajoka *et al*, 2017) and participate in the maintenance of physiological homeostasis by influencing the host immune system, metabolism of nutrients and protection against pathogenic microorganisms (Parker *et al*, 2019). The composition of gut microbiota is incredibly variable among different populations and may change from time to time in the same individual (Bäckhed *et al*, 2005; Qin *et al*, 2010). Many factors might affect the development of gut microbiota as host's age and genetics (Zoetendal *et al*, 2001), as well as other behavioural and environmental factors which include diet (Clarke *et al*, 2013), exercise (Kudelka *et al*, 2016), consumption

of antibiotics (Wawrzyniak *et al*, 2013) and smoking (Biedermann *et al*, 2013).

Intestinal microbiota most of them are occurred in colon, which gut microbial phyla are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* with *Firmicutes* and *Bacteroidetes* accounted up to 90% (Arumugam *et al*, 2011). Phylum *Firmicutes* includes *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus*, and *Ruminococcus* with *Clostridium* genera accounted up to 95% of all isolates. Also, phylum *Bacteroidetes* includes genera like *Bacteroides* and *Prevotella* (Rinninella *et al*, 2019). Phylum *Actinobacteria* has less number of bacteria dominated by *Bifidobacterium* genus (Bogitsh *et al*, 2015).

GI microbiota, contains essential genes, which are considered significantly more metabolic than other genes in the rest of human genome linked to different biochemical pathways by several specific enzymes (Barratt *et al*, 2011). they perform a variety of functions, including enzymes production for digestion and fermentation of unused energy substrates, vitamins such as vitamin K, bio-

tin and hormones which play important role in storing fats and plays important role in regulation of human biological process as epithelial development, modulation of metabolic phenotype and the effects of innate immunity (Zheng *et al*, 2019), as well as, affects the brain-gut communication of host's mental and neurological functions (Matijasic *et al*, 2020). Disturbance of gut microbiota or genes encoding may lead to unhealthy intestinal ecosystem or dysbiosis that affects health leading to different intestinal mucosal diseases as Crohn's disease, Ulcerative colitis and irritable bowel syndrome, and others as diabetes, obesity, cardiovascular and autoimmune diseases (Hills *et al*, 2019).

Soil-transmitted parasites are among the commonest infections worldwide estimated 1.5 billion infected people or 24% of the global population, mainly the poor and most deprived communities without piped water, sanitation and hygiene in tropical and subtropical areas, with the highest prevalence in sub-Saharan Africa, Asia, China, and South America (WHO, 2023). Parasites modulate hosts' feeding and reproduction behaviours by physiological pathways such as hormone, immunological and neuro-transmitters mediated mechanisms (Johnson and Nath, 2018).

Intestinal parasites infecting man are mainly *Enterobius vermicularis*, soil-transmitted helminthes, *Ascaris lumbricoides*, *Tricburis trichiura*, bookworms (*Necator americans/Ancylostoma duodenale*) and *Strongyloides stercoralis* and the protozoa *Entamoeba histolytica* and *Giardia duodenalis*. Others such as *Cryptosporidium* sp. and *Isopora* sp. are important in causing prolonged diarrhoea in immunocompromised patients (Norhayati *et al*, 2003). The multiple risk factors associated with these parasites, mainly poverty, poor sanitations, eating raw vegetables and contaminated water with bad drainage systems (Sejdini *et al*, 2011), using animal manures as fertilizers (Yahia *et al*, 2023). Parasites alter bacterial microbiota composition, modulate host's immune response, disrupting homeostatic relations between the bacteria and

the host (Naveed and Abdullah, 2021).

Gut microbiome affect more than 15 genera of different protozoa phyla; *Sarcomastigophora*, *Amoebozoa*, *Ciliophora*, and *Stramenopiles* (Hamad *et al*, 2016). About one-third of the world people were infected with *E. histolytica*, *G. intestinalis*, *Cryptosporidium* spp., *Toxoplasma gondii* and *Blastocystis* spp. altering the microbiota numbers (Burgess *et al*, 2017).

Giardiasis is caused by *Giardia intestinalis* affects millions of people with 280 million new annually (Ryan *et al*, 2019), associated with dysfunction in gastrointestinal barrier (Buret, 2007). The GI barrier impairment coupled with an increase in intestinal permeability was triggered by of myosin-light-chain kinase activation and elevation of intestinal enterocytes apoptosis (Troeger *et al*, 2007). In man, giardiasis leads to pathological changes, such as intraepithelial lymphocytosis, villous atrophy, granulocytes infiltration, lymphocytes, plasma cells into lamina propria, and nodular hyperplasia (Koot *et al*, 2009). Disruptions of commensal microbiome may contribute to a number of acute, chronic, and post-infectious clinical pictures manifestations of giardiasis and may account for variations in disease presentation and /or between infected populations. (Fekete *et al*, 2021). This supported the bidirectional relationship between parasites and microbiome that influence resistance and susceptibility to the *Giardia* colonization (McGregor *et al*, 2023). Microbiota distribution by antibiotics restricted disaccharides efficiency and inhibited CD8+T cell activation, but didn't modify lamina propria proportion receptor-expressing lymphocytes (Allain *et al*, 2018). Thus, bacteria influence activation of CD8 + T lymphocyte by acute infection showed the microbiota importance and giardiasis potential therapy (Keselman *et al*, 2016).

Cryptosporidium is an infectious opportunistic protozoan with more than 30 species with *C. parvum* and *C. hominis* infect man (Pane and Putignani, 2022), by ingesting of oocysts in stools, raw food and/or water or

animal-to-person or person-to-person (Putignani, 2021). *Giardia* and *Cryptosporidium* infective stages were recovered from polluted water canals (El Shazly *et al*, 2007). It is common in countries with over-crowding, and infected livestock (Bouzid *et al*, 2018). Most cases are asymptomatic or self-limited, or chronic threatening immunocompromised individuals, such as AIDS, HIV, or on immunosuppressive drugs (Gerace *et al*, 2019). Also, infection is very common in patients with dysbiosis or dysregulated microbiota (Ras *et al*, 2015). Parasite invades small intestinal epithelial cells alter the gut microbes producing metabolites (Karpe *et al*, 2021). These metabolites are used as nutrients for parasite metabolism (Khan *et al*, 2021). On microbiota depletion, *Cryptosporidium* caused high burden (Charania *et al*, 2020). Also, its ability to infect the gut is affected by the age-related changes in gut microbiota or in diet (Thomson *et al*, 2017). In Egypt, human cryptosporidiosis prevalence was 49.1%, of which 60.5% were *C. hominis*, 38.2% *C. parvum* and 1.2% *C. parvum* plus *C. bovis* (Helmy *et al*, 2013). Among children with diarrhea, *C. hominis* was relatively more common in children than *C. parvum* (Mohammad *et al*, 2021).

Amebiasis histolytica: Generally, the majority of infections restricted to the intestinal lumen (luminal amebiasis) are asymptomatic. Amebic colitis, or invasive intestinal amebiasis, occurs when the mucosa is invaded. Symptoms include severe dysentery and associated complications. Severe chronic infections may lead to more complications such as peritonitis, perforations, and amebic granulomas formation (ameboma). Amebic liver abscess is the common manifestation of extraintestinal amebiasis. Pleuropulmonary abscess, brain abscess, necrotic lesions on perianal skin and genitalia have occurred (CDC, 2015).

The trophozoites proliferate in intestinal lumen and phagocytose gut flora like *Lactobacillus ruminus* (Iyer *et al*, 2019). *E. histolytica* pathogenicity is linked to its interac-

tion with gut microbiota (Burgess and Petri, 2016). Bacteria with the appropriate recognition molecules are ingested by the parasite (Bracha and Mirelman 1984). *E. histolytica* feeds on certain bacteria species allowed the other species to proliferate (Bansal *et al*, 2004). Faecal microbiota composition was used as tool of *Entamoeba* colonization with 79% accuracy (Morton *et al*, 2015). Also, commensal *Enterobacteria*, with the derived metabolites as oxaloacetate and queuine play the protective role against oxidative stressing the trophozoites (Shaulov *et al*, 2018). The molecular mechanisms of bacterial protection showed three keys. 1- *Enterobacteriaceae* alter transcription of many of the amoebic genes affecting about 31% of coding sequences (Guillén, 2023), including genes related to protein synthesis (homeostasis, nutrition, cell survival, encystation factors, and many anti-oxidant enzymes. 2- Oxaloacetate acts as a non-enzymatic anti-oxidant and hydrogen peroxide scavenger, reduced proteins oxidized level (Varet *et al*, 2018). 3- Queuine, a hyper-modified nucleobase, induced hyper-methylation of the specific tRNAs, impacting protein synthesis, and queuine up-regulated genes encoding anti-stress proteins as heat shock protein 70, anti-oxidant enzymes and DNA repair enzymes (Nagaraja *et al*, 2021). Protective effect of *Enterobacteriaceae* on *E. histolytica* was not universal, as *L. acidophilus* produces hydrogen peroxide modifying amoebic transcriptome differently compared to *Enterobacteriaceae*. *L. acidophilus* induces oxidation of vital proteins in *E. histolytica* including Gal/GalNAc lectin heavy chain, thioredoxin, cysteine protease A5, oxidoreductases, and signaling molecules, led to parasite death (Sarid *et al*, 2022). Certain bacteria as *Clostridia* inhibits *Entamoeba* growth (Burgess *et al*, 2016).

Blastocystis spp. was generally associated with higher gut bacterial diversity in composition of a healthy microbiota (Kodio *et al*, 2019). But, it reduces the beneficial bacteria (Nourrisson *et al*, 2014), related with irrita-

ble bowel disease (Shirvani *et al*, 2020) and the bowel inflammatory (Peña *et al*, 2020), mainly *Bifidobacterium* and *Lactobacillus* (Tito *et al*, 2019). *Blastocystis* subtypes (ST) are 22, but only ST1 to ST9 were reported in man with ST1-4 up to >90% (Stensvold *et al*, 2020). *Blastocystis* and dysbiosis showed that pathogenicity was subtyped dependent (Deng *et al*, 2021). The in-vitro co-incubation assay showed that bidirectional impact between *Blastocystis* and different gut bacteria but, ST7 cell was higher in them with discriminating effect on specific groups; enhanced *Escherichia coli* growth and reduced *B. longum* and *Lactobacillus* spp. (Yason *et al*, 2019). In Egypt, the most prevalent protozoal parasites were *Blastocystis*, followed by *E. histolytica* complex, and *G. intestinalis*, with age, sex, living in a rural areas, and water source were all the potential risk factors for intestinal parasitism (El-Wakil *et al*, 2023).

Toxoplasma gondii is a zoonotic parasite affecting nucleated cells of many mammals and birds hosts and infected by consuming contaminated food and water (Almeria and Dubey, 2021). Also, *T. gondii* nosocomial infections occurred by the needle stick injury (Saleh *et al*, 2017) or blood transfusion (Morsy *et al*, 2022), as antibodies were reported in blood donors in Saudi Arabia (Sarwat *et al*, 1993), and in Egypt (Elsheikha *et al*, 2009). Besides, anti-*T.gondii* antibodies were reported in milk of farm animals in Port Said (Rifaat *et al*, 1969) and in donkeys in Greater Cairo (Haridy *et al*, 2010). Congenital toxoplasmosis led to critical anomalies (Liu *et al*, 2015) including abortion, encephalitis, enteritis, stillbirth or neonatal death or later chorioretinitis (Abbas *et al*, 2020).

Complex interactions are between *T. gondii* mucosal immune system and microbiota (Snyder and Denkers, 2020), by modifying microbiota of mice in acute and chronic infection (Shao *et al*, 2020) by secreting relevant factors while invading intestinal tissue causing microbiota changes (Partida-Rodríguez *et al*, 2017). In mice orally infected with

T. gondii intestinal microbiome showed that ileitis increased bacterial load, decreased species diversity, and translocation by a significant reduction or disappeared of *Bacteroidetes* and *Firmicutes* (Raetz *et al*, 2017). Microbiota co-evolved with the host intestinal immune system plays marked role in expressing regulatory immune mediators and in developing and differentiating immune cells (Sjögren *et al*, 2009). The metabolites excreted by gut microbiota affect the parasites physiology and survival status leading to a different infection course (Berrilli *et al*, 2012). The misuse of antibiotics can eliminate intestinal bacteria, so generated germ-free mice might show no intestinal inflammatory reaction against *T. gondii* and gut microbiota can cure parasitosis as probiotic treatment or microbiota transplantation approved to cure the infection (Yan *et al*, 2022).

Helminths and gut microbiome: GIT worms can survive for long time causing alteration in the intestinal physiology, permeability and mucous secretions that altered the gut microbiota composition (Zaiss and Harris, 2016). *Ascaris* stimulates an increase of facultative anaerobes such as *Streptococcus* which provide a highly suitable metabolic environment to its survival and reproduction, and suppresses anaerobic ones as *Faecalibacterium* and *Ruminococcus* which are essential for the proper functions of intestine, but increase in *Prevotella* spp., *Bacteroidetes* to *Firmicutes* and *Clostridia* in the F/B ratio was strongly associated with helminths to induce metabolic changes to promote infection (Williams *et al*, 2021). But, *Necator* spp. and *Trichuris* spp. have beneficial effect on gut microbiota by decreasing *Lactobacillus* and *Lachnospiraceae* species associated with sepsis especially in immunosuppressed patients (Sedzikowska and Szablewski, 2021). *Allobaculum* and *Olsenella* are intestinal arachidonic acid metabolizing bacteria causing intestinal inflammation positively associated with soil-borne helminthes. Yousof (2023) in Egypt reported that helmi-

nths have the positive impact by expanding bacterial populations that produce short-chain fatty acids, enhancing host's health status. Arachidonic acid is the precursor of pro-inflammatory leukotrienes that threatens survival of helminths (Wood *et al*, 2008).

Enterobius vermicularis in children was associated with an increase of *Bifidobacterium longum* but decrease in *Fusobacteria* and with Mebendazole, there was an increase in *Actinobacteria* phylum, including probiotic *Bifidobacterium*s, and *Streptococcus thermophilus* (Yang *et al*, 2017). Enterobiasis or pinworm was reported worldwide mainly in preschool & school aged children, but any individual is susceptible to infection (Mohamed, 2022). First evidence of infection was from Roman-occupied (30BC-AD395) Egypt (Horne, 2002). The worms may also migrate from the anus along female patient genital organ and pass with urine (Powell *et al*, 2013), or the worms infect the appendix and mimic appendicitis (Zaghlool *et al*, 2015). Man is the only known host, but occasional infections were in chimpanzees and rabbits (CDC, 2011).

The blood sucking hookworms increased the diversity of gut microbiota caused by infection helps in reducing inflammation by restoring the microbes balance and immune system (Giacomin *et al*, 2016). In a mice experimental study, infection with hookworm *Nippostrongylus brasiliensis*, showed significant changes in gut microbiota, such as decreased *Turicibacteriaceae* and *Candidatus arthromitus* and increased *Lactobacillaceae* populations. These microbial changes were associated with the initiation of a Th2-mediated immune response against hookworms, involving IL-13-mediated alterations in intestinal mucus, production of antimicrobial peptides, and a reduction in proinflammatory IL-17-encoding transcripts (Fricke *et al*, 2015). This gave a complex interplay between the gut microbiota, Th2 immune response, and host defence mechanisms in helminthic infection (Beyhan and Yıldız, 2023). Besides, helminthic infections are known for

immunomodulatory effects by secreting multiple excretory-secretory products such as glycoproteins and microRNA that promote functions of various immune cell types and cytokines as IL-13-mediated changes intestinal mucus reducing pro-inflammatory IL-17; and chronic ones help in controlling allergic and autoimmune diseases (Maizels, 2009).

In Egypt, animal reservoirs of parasitic zoonosis were identified, including rodents, stray dogs, and cats as well as domestic and farm animals and birds (Ismail *et al*, 2018).

Autoimmune diseases (ADs) are characterized by unregulated immune responses to self-antigens causing the chronic inflammation (Bach, 2014). Both genetic and environmental risk factors have been involved in the advance of ADs, over the past decade, the alterations in the composition of the gut microbiota, which are closely associated with lifestyle changes and more ADs (Song, 2018).

Next-generation sequencing (NGS) techniques showed that the gut microbes genes exceeded human ones by ~150-fold and they established unique metabolic activities (Qin *et al*, 2010). Epidemiological data showed the inverse correlation between the parasitic prevalence and the incidence of autoimmune diseases (Fleming and Fabry, 2007). The helminths have co-evolved with hosts creating immunological privilege and immune tolerance (Dunne and Cooke, 2005). Thus, animal models verify helminthic infections have an ability to prevent autoimmune diseases in diabetes type-1 (Hubner *et al*, 2009), multiple sclerosis (Sewell *et al*, 2003) and colitis (Xu *et al*, 2019).

The safety and efficacy of probiotic worm therapy in chronic inflammatory conditions and autoimmune diseases. *Necator americanus* larvae assessed inflammatory bowel disease (Croese *et al*, 2006), asthma (Feary *et al*, 2010) and celiac disease (Croese *et al*, 2015). Navarro *et al*. (2016) reported that in the developed countries, decreased prevalence of some parasitosis were due to increased allergic incidence and autoimmune dis-

orders. They added that recombinant hookworms' anti-inflammatory protein-2 (AIP-2) served as a curative therapeutic for the allergic asthma and inflammatory diseases.

Conclusion

The relationship between human gut microbiome and intestinal parasites is complex with positive or negative effects. In dysbiosis, disruptions of gut microbiome exacerbate the pathology associated with parasites,

Also, gut microbiome plays a crucial role in shaping immune response. Balance and diversion of microbiome is a must to have immune homeostasis and marked responses against all pathogens, including parasites.

Recommendation

Human digestive-tract associated microbes are referred to as the gut microbiome. It is crucial that research in this domain is a continuous process, and knowledge between gut microbiome and these parasites is on-going the constant evolution.

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