Minireview

Comorbidities involving parasitic diseases: A look at the benefits and complications

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Impact Statement

In recent years, advances in and the acquisition of knowledge about parasites and associated diseases, even those considered neglected tropical diseases, have been achieved. These studies have allowed a better understanding of diseases caused by parasites, the intrinsic aspects of parasite biology, and the impact on human development. In addition, new approaches have emerged to elucidate the impact of parasitic diseases on morbidities worldwide. Experimental and epidemiological findings have demonstrated that parasitic infections co-occurring with cancer or metabolic diseases may not only alter disease progression but also aid in the search for new therapeutic molecules obtained from parasites to treat such morbidities. In this review, we discuss important aspects of comorbidities associated with parasitic diseases and highlight possibilities for future research aimed at discovering new therapeutic targets for cancer and metabolic diseases.

Abstract

Parasitic infections acquired by the population cause substantial morbidity worldwide, with individuals from developing countries being most affected. Some parasites remain in the host for long periods, settling in different organs, manipulating the flow of nutrients and metabolites, and influencing the immune response, favoring their adaptation. The host attempts to counteract the metabolic and immunological alterations and the possible damage caused by infection. These metabolic and immunological changes experienced by the host can influence the progression of other existing morbidities or those that will be acquired in the future. Cancer and metabolic diseases are also frequent causes of morbidity in the world population. The large numbers of individuals affected by cancer and metabolic diseases and the high prevalence of morbidity caused by parasitic diseases favor the development of comorbidity involving these pathologies. This review provides an overview of major advances in research on cancer and metabolic diseases associated with parasitic infections. Information about hosts and parasites such as alterations of the immune response, metabolism and adaptation mechanisms of the parasites, and parasitic molecules with therapeutic potential is provided, as well as the beneficial results or complications related to the comorbidities discussed herein. We emphasize the need to conduct additional studies addressing comorbidities associated with parasitic infections to improve the understanding of the impact of this association on the progression of morbidities, as well as the possibility of the therapeutic use of and therapeutic approaches involving parasites.

Keywords: Comorbidities, parasitic diseases, cancer, metabolic diseases

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Introduction

Infections by protozoans and helminths cause high morbidity rates worldwide, mainly affecting individuals in developing countries.[1–3] Some of these parasites can survive in a host for a long period of time. Studies have reported that regulation of the host's metabolism and immune system is key to the success of this harmonious co-existence.[4,5]

Parasites capable of remaining in a host for prolonged periods settle in different organs and manipulate the flow of nutrients, the production of metabolites, and the immune response according to their needs, favoring their adaptation.[4] However, the host organism attempts to compensate for the metabolic and immunological alterations and possible damage caused by this co-existence. As a response to these changes, the host can change the way in which it responds to an existing morbidity or one that will be acquired later; both of these conditions are considered comorbidities.

Cancer causes morbidity and should receive more attention in studies on parasitic diseases. Studies show that there are more than 18.1 million cancer cases and 9.6 million cancer-related deaths annually worldwide.[6,7] The high rates

of cancer and diseases caused by protozoan and helminth parasites that affect the human population allow for the frequent co-existence of these two conditions. This scenario demonstrates the need for direct studies to improve the understanding of how the human body responds to cancer when a parasitic disease is also present, and vice versa.

Immunometabolism research, linking metabolism with the immune response, in those with parasitic infections is an emerging field. The magnitude and clinical implications of metabolic syndrome, considered an immunometabolic imbalance, in association with parasitic infection have been an important research topic.[5,8]

In this minireview, we will address cancer and metabolic syndromes associated with infections and diseases caused by protozoans and helminths. We will provide information about the host immune response, changes in metabolism, and the outcome of this association.

Cancers and parasitic diseases

Cancer comprises a series of diseases caused by the production of neoplastic cells. Carcinogenesis is complex and is likely caused by genetic or environmental factors, but infectious and parasitic diseases can interfere, favoring or modulating carcinogenesis.

Cancers have the biological properties that contribute to the immortality of neoplastic cells. Certain parasites have the potential to change these properties, as they can modify the host immune response and consequently modify the tumor microenvironment. Some neoplastic cells can evade the immune response, preventing their recognition and elimination.[9] Seeking to improve the antitumor immune response, studies on immunotherapy targeting tumors have shown promising results for the treatment of cancer. Certain protozoans and helminths have been shown to be potential targets for future research on antitumor immunotherapy, as they have shown the ability to reactivate or improve the immune response of patients with certain neoplasms.

Cancers associated with protozoan infections

Toxoplasma gondii (*T. gondii*) is an intracellular protozoan that causes toxoplasmosis and has the potential to modulate the host immune response and induce an antitumor response. This parasite is intracellular, and to ensure survival, it induces a strong Th1 response, with increased production of interferon gamma (IFN)-γ and interleukin (IL)-12.[10,11] Baird *et al.* treated melanoma in a murine model with intratumoral injections of an attenuated strain of *T. gondii* and observed increased production of CD8+ T cells and natural killer (NK) cells. These modifications in the tumor microenvironment induced the regression of primary melanomas and reduced the risk of tumor recurrence.[12] Another research group demonstrated that active infection of *T. gondii* increased survival in mice challenged with Lewis lung carcinoma cells, in addition to inhibiting tumor growth through antiangiogenic activity and the induction of a Th1 immune response.[11]

Chen *et al.* found that infection by *Plasmodium* sp., an intracellular protozoan species that causes malaria, induces a potent innate and adaptive antitumor immune responses, thus promoting survival and reducing the proliferation of Lewis lung carcinoma cells in an experimental model. Infection by *Plasmodium* sp. increased the production of IFN-γ and tumor necrosis factor (TNF)-α and the activity of NK cells and stimulated the cytolytic activity of $CD8^+$ T cells, thus generating reductions in the size of the tumor and the number of metastases.[13]

Epidemiological studies have demonstrated that patients infected with certain parasites have a lower incidence of certain tumors. Garcia *et al.* suggested that *Trypanosoma cruzi* (*T. cruzi*) infection increases immune activity, and thus has an important role in prevention of the development of colon tumors.[14] Other studies have suggested that infection with *T. cruzi* or the use of molecules from this parasite induces antitumor effects. The reports suggest that *T. cruzi* calreticulin alters the tumor microenvironment, causing neoplastic cells to be exposed to the immune system, thus hindering carcinogenesis.[15] Calreticulin can also induce an antiangiogenic effect on breast tumors due to its ability to inhibit endothelial cell proliferation.[16]

Ubillos *et al.*, using experimental models of human carcinogenesis, observed that *T. cruzi* epimastigote extract powerfully inhibited the development of breast and colon tumors through the activation of $CD4^+$ and $CD8^+$ cells. The tumor-associated immune response induced increases in the numbers of macrophages and dendritic cells as well as increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity.[17] In addition to inducing activation of the immune system, proteins from *T. cruzi* demonstrated proapoptotic activities in several cell lines. A recombinant protein based on the *T. cruzi* surface molecule gp82 fused to glutathione-S-transferase induced apoptosis in melanoma cells without generating changes in healthy melanocytes. Mice treated at the site of the tumor had smaller tumor masses and longer survival times than untreated animals.

Interestingly, *T. cruzi* has paradoxical characteristics, as it has antitumor as well as carcinogenic properties.[18] Patients with Chagas disease (CD) usually develop a severe inflammatory response and can experience cell destruction and/or proliferation, which, under chronic conditions, can result in the occurrence of neoplasms.[19] Approximately one-third of patients with CD will develop irreversible digestive disorders, with megaorgan syndrome being the most common.[20] Megaesophagus is a condition that occurs in patients with CD, and it is related to an increased prevalence of esophageal cancer. The mechanism associated with this increased prevalence is gastroesophageal reflux into the megaesophagus.[21]

Although malaria is not considered a carcinogenic disease, infection with one of the protozoans that causes malaria, *Plasmodium falciparum*, in patients with the Epstein–Barr virus infection increases the risk for Burkitt's lymphoma, which is an aggressive non-Hodgkin B-cell lymphoma.[22] The mechanisms by which malaria increases the risk of this cancer and how malaria induces the pathogenesis of Burkitt's lymphoma are still unknown.

Cancers associated with helminthic infections

Echinococcus granulosus (*E. granulosus*) is a helminthic parasite; the adult form parasitizes the intestines of domestic dogs and wild canids, while the larval form infects herbivores

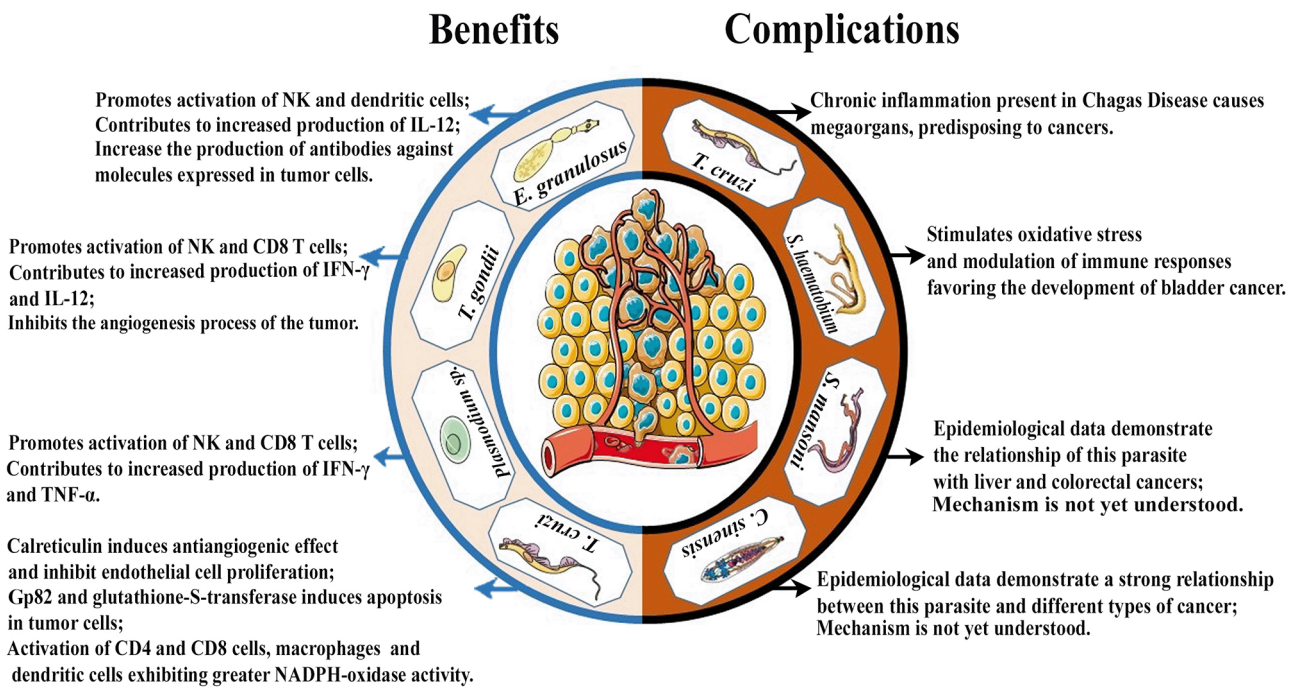

Figure 1. Influence of parasitic infection on tumor development. (A color version of this figure is available in the online journal.)

and, accidentally, humans. The studies have demonstrated that *E. granulosus* has antigenic properties similar to those of mucin peptides, is able to promote the activation of NK cells and mature dendritic cells, and can increase the production of IL-12, which are important targets of antitumor therapies.[23–26] Corroborating the results of the previous study, another study reported that mice inoculated with human hydatid cyst fluid presented tumor regression in a colon cancer model and developed antibodies capable of recognizing mortalin and creatine kinase M-type expressed by neoplastic cells, thus reducing tumor proliferation.[27]

Schistosomiasis is caused by helminths of the genus *Schistosoma* and is considered the most prevalent human helminthiasis. This disease is associated with the presence of snails, which are intermediate hosts, in the environment and inadequate levels of basic sanitation. Adult worms infect humans, and parasite excretions, secretions, and eggs are involved in the induction of carcinogenesis. Among the *Schistosoma* species, chronic infection with *Schistosoma haematobium* (*S. haematobium*) is classified as carcinogenic by the International Agency for Research on Cancer.[28] This species causes urogenital schistosomiasis and is associated with the development of urinary bladder cancer. A recent study performed a proteomic analysis of urine samples from patients infected with *S. haematobium* and verified the involvement of oxidative stress and immune responses as mechanisms of bladder cancer development associated with urogenital schistosomiasis.[29,30] *Schistosoma mansoni* (*S. mansoni*) infection in those with hepatitis C virus infection is considered a risk factor for the occurrence of hepatocellular carcinoma. Furthermore, the altered expression of tumor protein 53 in patients with colorectal cancer-related *S. mansoni* colitis suggests that schistosomiasis may induce carcinogenesis.[31]

Clonorchiasis is a liver disease caused by the trematode *Clonorchis sinensis* (*C. sinensis*). In general, the infection is acquired by eating raw or undercooked freshwater fish. The association of this parasite with the development of cholangiocarcinoma is well documented, and for this reason, *C. sinensis* has been classified as a highly carcinogenic agent.[32] The mechanisms by which this parasite influences carcinogenesis are still not fully understood; however, it has been suggested that physical damage and inflammation are pathways with high carcinogenic potential.[30]

Tumors and parasites are autonomous and utilize certain mechanisms for their survival; biological similarities between parasites and cancer have already been noted. These similarities have high potential for exploitation in the fields of both parasitology and medicine. It is known that some parasites can cause cancer; however, certain molecules and survival mechanisms of parasites can help in the treatment of cancer (Figure 1). For this reason, further studies that aim to identify additional carcinogenic factors in parasites and which immunological mechanisms contribute to the modulation or promotion of carcinogenesis are necessary. Investing in research on this subject can simultaneously improve the treatment and prevention of cancer and parasitic diseases.

Metabolic and parasitic diseases

Metabolic syndrome is characterized by the accumulation and dysfunction of adipose tissue (AT), consequently leading to insulin resistance (IR), which causes atherosclerotic cardiovascular disease, diabetes mellitus (DM), and vascular and neurological complications, such as hypertension and stroke, due to overweight, obesity, a lack of physical activity, or genetic predisposition.[33,34] Therefore, metabolic syndrome is not a definitive disease, but rather a series of risk factors that induce a complex pathophysiological state.[35]

Obesity and overweight have reached epidemic proportions worldwide and are, in fact, real epidemic and public health

problems.[36] According to the World Health Organization, more than 1 billion people are overweight worldwide, of which 300 million are obese. The prevalence of obesity is higher in female than in male and can increase with increasing age.[37] Obesity affects different organs and shortens life expectancy. It is a condition related to high body mass index (BMI), which is a risk factor for an increasing number of chronic diseases, including cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, different types of cancer, and type 2 diabetes mellitus (T2DM).[38,39] The inflammation that occurs in AT in obese individuals is the main mechanism driving the development of IR and T2DM. However, under obesity conditions, the stimulation of the host immune response to T2DM seems to promote AT homeostasis and adaptation to stress, with a dual role.[40,41]

DM is a multifactorial chronic health condition characterized by high blood glucose levels. Deficiency in the production or function of insulin or both is the cause of metabolic disorders, which can occur for different reasons, resulting in protein and lipid alterations.[42,43] Individuals affected with type 1 diabetes mellitus (T1DM) are not able to produce enough insulin. In this type of DM, β cell destruction occurs in the pancreas, thereby hindering the release of insulin. T2DM is linked to complex metabolic disorders and to increased morbidity and mortality.[44] The insulin response is reduced, inducing IR. Initially, the production of insulin by β cells in the pancreas increases to ensure glucose homeostasis, but over time, there is a decrease, resulting in T2DM, which accounts for approximately 90% of all cases of DM in individuals over 45 years of age.[45]

Studies on the association of metabolic syndrome with parasitic infections are scarce in the literature. However, the large number of individuals with metabolic syndrome who are exposed to parasitic infection demonstrate the importance of further investigations in this field to elucidate the magnitude and clinical implications of morbidities associated with parasitic infection.

Metabolic diseases associated with protozoan infections

The cause-and-effect relationships of protozoan infections with metabolic diseases, such as obesity and diabetes, still need to be further elucidated. Studies have demonstrated that protozoan infections can cause lipid and glycemic alterations and can influence the immunometabolic regulation or dysregulation of the host.[8,46] de Carvalho *et al.* studied the effects of *Plasmodium berghei* infection in obese C57BL/6 mice. In this study, it was found that obesity contributed to a lower level of parasitemia in obese mice than in control mice, and this result was associated with a substantial increase in the production of cytokines, including regulatory profile IL-10, proinflammatory IL-12, TNF-α, and IFN-γ.[47] In fact, in those with malaria, a delicate balance between proinflammatory and regulatory cytokine production is necessary for the destruction of the parasite and the prevention of serious complications.[48–50]

In contrast with the benefits observed in obese mice experimentally infected with *P. berghei*, which were discussed previously, *P. falciparum* infection in humans causes severe malaria in obese individuals and those with metabolic risk factors, such as DM.[51] These observations suggest that factors intrinsic to the parasite species, in addition to differences in clinical manifestations caused by both species, influence or are differentially affected by metabolic disease conditions. Malaria is diabetogenic risk factor in obese individuals when associated with oxidative stress and inflammation, leading to IR and to the development of DM.[52]

Amoebiasis, caused by the protozoan *Entamoeba histolytica* (*E. histolytica*), is considered the most serious protozoan intestinal disease.[53] When present in T2DM patients, it can induce severe amoebic colitis due to the microangiopathy that occurs in diabetic patients.[54] Microangiopathy caused by T2DM, mainly affects blood vessels in the retinas and kidneys and also compromises small vessels in the intestinal wall, restricting the inflammatory response against amoebic trophozoites, resulting in greater tissue damage. This relationship is supported by studies that found that immunosuppression caused by diabetes was observed in more than 50% of patients with amoebiasis, reinforcing the need for the diagnosis of T2DM in endemic areas to guide therapeutic management in those infected.[55,56]

Evidence of the mechanism of action of *T. cruzi* infection under obesogenic and DM conditions has already been documented. A cross-sectional observational study evaluated 361 individuals with an overall mean age of 60.7 years who presented with chronic CD and had migrated from rural to urban centers. The results demonstrated that the percentage of individuals with metabolic syndrome was 40.4%, and the prevalence of hypertension, dyslipidemia, obesity and DM was 67.3%, corroborating the high prevalence of metabolic syndrome in patients with CD.[57] Another cross-sectional study that investigated epidemiological, clinical and molecular aspects in 283 individuals aged 35–74 years demonstrated a prevalence of metabolic syndrome of 48.2% in patients with CD; however, despite results similar to those in the previous study, the results of DM were different. Even with higher glycemic indices among individuals positive for CD, there was no dependent association between DM and CD positivity on serology. These results suggest that *T. cruzi* infection in AT and the pancreas in CD patients is not related to important glycemic changes.[58]

Cutaneous leishmaniasis (CL) caused by *Leishmania brasiliensis* (*L. brasiliensis*) was studied in patients with obesity associated with glucocorticoid therapy. In this study, the authors stated that obesity modified the clinical characteristics of CL via the host immune response, as patients developed hypertrophic ulcers instead of typical oval ulcers. In addition, there was a direct correlation between BMI and a prolonged healing period. Obese patients had high levels of the hormone leptin, which the authors believe contributed to not only the severity of the disease but also the low efficacy of therapy compared with overweight patients with a normal BMI.[59] A similar relationship was found when the same disease was studies in patients with DM. Changes in immunological, biochemical, and hematological parasitological factors were associated with a significant increase in the number of cases and duration and size of lesions in patients with and without DM.[60]

Regarding visceral leishmaniasis (VL), it was verified in C57BL/6 mice with induced obesity and subsequent

infection with *Leishmania infantum* that obesity contributed to an increase in the parasite load in the liver and spleen when compared to the control diet group. Furthermore, increases in the production of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-6, and nitric oxide, and reductions in the production of regulatory cytokines IL-10 and transforming growth factor (TGF)-β, which are related to inflammation and cell hyperplasia, were observed, confirming that under obesity conditions, the parasite can prevent the induction of protective immunity against *Leishmania* infection.[61]

Human toxoplasmosis occurs mainly through the ingestion of oocysts of *T. gondii* present in contaminated vegetables and water; currently, ingestion is the most frequent route of transmission, as there has been an increase in the consumption of healthy foods due to changes in eating habits in the last 20 years.[62] The association between chronic toxoplasmosis and DM was recently evaluated in a study in 105 diabetic individuals, including 36 with T1DM and 69 with T2DM. The authors highlighted that *T. gondii* infection was significantly associated with T1DM (69.4%) and T2DM (72.5%) and the need for further investigation into the exact mechanisms of these associations. In addition, the main risk factor for *T. gondii* IgG seroprevalence in patients with T2DM and without DM was contact with cats.[63]

Another recent study conducted by Al-Khafajii *et al.*[64] assessed toxoplasmosis positivity in relation to BMI in patients with diabetes and metabolic syndrome, including obesity, overweight, normal weight, diabetes, non-diabetes, obesity-diabetes, obesity-non-diabetes, overweight-diabetes, overweight-non-diabetes, and normal weight-non-diabetes, and found that the rate of *T. gondii* seropositivity showed no significant difference among the study groups. Indeed, it is necessary to expand and develop experimental and human studies on *T. gondii* infection under the conditions of DM and obesity to identify other variables that can induce favorable or harmful events.

Metabolic diseases associated with helminthic infections

Epidemiological studies have demonstrated high rates of helminth infections in communities in developing countries and that such infections are inversely correlated with autoimmune or inflammatory diseases, such as obesity and metabolic syndrome.[40] The result of co-evolution between host and parasite has resulted in survival of helminths in hosts due to a reduced anti-inflammatory effect of helminth infection attributable to immunomodulatory action of the type 2 response.[65] Indeed, this modulation of the inflammatory process by the type 2 response during helminth infection may delay the development of T2DM and alter lipid profiles. Rajamanickam *et al.*[66] evaluated the immunological response to helminth (*Strongyloides stercoralis*) infection in those with T2DM and without DM and found that the plasma levels of anti-inflammatory Th2 cytokines (IL-4, IL-5, and IL-13) were significantly elevated in individuals with T2DM, resulting in positive modulation of glycemic parameters.

Other studies in humans with co-infection with different species of helminths (*S. mansoni*, *Trichuris trichiura*, hookworm, and *S. stercoralis*) demonstrated that the causal relationships between parasite infection and lipid profiles are favorable for reducing cholesterol, thus improving the lipid profile.[67,68] Regarding the association of obesity and helminth infection, infection contributes to an improvement in the clinical condition of overweight.

Clinically, obesity and DM, especially uncontrolled obesity and DM, cause health problems that affect the quality of life of individuals. Although some reports have demonstrated beneficial effects of relationships between metabolic diseases and parasitic infections, other studies demonstrated that these relationships can sometimes be altered under certain conditions, aggravating the clinical condition. Intestinal parasitic infection by *Ascaris lumbricoides* (*A. lumbricoides*) in those with obesity in childhood and during puberty can have an effect on metabolism by altering the composition of the intestinal microbiota, which is related to an increased probability of the development of overweight or obesity with increasing age in these individuals.[69]

The relationship of DM with intestinal parasite infection has previously been elucidated. It was reported that individuals with DM with uncontrollable glucose levels exhibited an increase in susceptibility to intestinal parasites, with *A. lumbricoides* and hookworm being the predominant helminths and *Giardia lamblia* being the predominant protozoan. In this study, the authors concluded that the most common parasite in individuals with DM was *G. lamblia* (47.9%) and that the uncontrollable blood glucose level in these patients decreased the efficiency of the immune system, resulting in a higher predisposition to intestinal parasites.[70]

Human toxocariasis, caused by the nematode *Toxocara* spp., is an endemic parasitic anthropozoonosis, and its risk factors are contact with dogs and cats, living in a rural area and consuming raw or undercooked animal meat.[71,72] It is considered one of the most widespread parasitic zoonotic infections, as it can spread among humans, domestic dogs, wild canids, and probably other mammals.[73]

To contribute to new diagnostic and vaccination strategies, a proteomic study of excretory and secretory proteins of *T. canis* in the larval stage identified 19 proteins associated with protein binding functions, inorganic ions, and organic compounds.[74] To achieve a deeper understanding of parasite metabolism, non-protein products were investigated in *T. canis* in the adult stage. Sixty-one biomolecules were identified, of which forty-one polar metabolites, fourteen medium-long-chain fatty acids, and six short-chain fatty acids were correlated with corresponding biological properties described in the literature, including anti-inflammatory, antimicrobial, antidiabetic, healing, laxative, antiaggregant, antiarrhythmic, and hypolipidemic properties; in addition, these biomolecules were associated with the prevention of diseases such as hypertension, T2DM, and coronary heart disease.[75] The biological properties of a parasite can provide protection for the parasite and also benefit the host by inducing metabolic changes, although the reasons for this remain unknown. It has not been considered that parasitic infection can resolve the physiological dysfunction caused by metabolic syndrome, but it has been recognized as a preventive factor for certain diseases in the context of parasite–host interactions.

Helminth infection and associated immune modulation have been extensively studied. Th2 cells have been described

as crucial in adaptive immune responses to extracellular parasite infections, as they stimulate dendritic cells to induce costimulatory signals to initiate of a protective response as well as a typical response at the site of infection.[76,77] Studies in humans and obese animals have reported the relationship of helminth infection with improved metabolic function, which can be positive when it results in improved IR or a reduction in the risk of T2DM.[78–82]

T. trichiura is an intestinal nematode species that is predominant in communities with poor sanitary conditions; it is a soil-transmitted helminth (STH) that causes trichuriasis, which causes adverse daily life conditions, such as compromised school performance.[83,84] Specifically, parasitic infection with *T. trichiura* and co-infection with other parasites was studied in rural workers in Indonesia who had elevated lipid, blood glucose, and blood pressure levels. In total, 424 participants infected with at least one species of helminth were compared to 222 uninfected participants, and 19.7% were infected with *T. trichiura*. Those workers with parasitic infection had a lower BMI, glycemic rate, low-density lipoprotein (LDL) cholesterol level, and total cholesterol level than those without STH infection. However, to correlate innate and adaptive immune responses, inflammation, STH infection, and insulin sensitivity in humans, additional information is essential.[78]

Considering that the above-mentioned parasitic diseases are still considered neglected diseases, further studies with a broader scope are needed to analyze associations between such diseases and various pathophysiological changes in metabolic syndrome; the results could elucidate information that contributes to not only the prevention of these diseases but also the treatment of affected populations.

Conclusions

Comorbidities of parasitic diseases occur frequently because humans are exposed to a large number of parasites. A better understanding of how infections and parasitic diseases affect the pathophysiology and progression of common morbidities is necessary. Moreover, several studies discussed herein suggest that some parasites can be studied as therapeutic agents for some types of cancers and metabolic diseases. However, there are still many questions, and the conflicting results of different studies indicate the need to direct efforts toward a better understanding of the impact of parasitic diseases on morbidities that affect people. Indeed, parasites have evolved over the years, and some have adapted to resist human host defenses. The complexity of this adaptation from a biological standpoint can alter the way the humans respond to the possible co-existence of morbidities.

AUTHORS' CONTRIBUTIONS

FMSO and MVC conceptualized and designed the study and take responsibility for the integrity of the data. FMSO, REC, GRGP, and MVC contributed to the writing of the report. FMSO and MVC contributed to critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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