Endotext

HELMINTHS AND ENDOCRINOLOGY

Nishant Raizada, MBBS, MD, DM Endocrinology
Associate Professor, Department of Endocrinology, University College of Medical Sciences, New Delhi, India. drnishantraizada@gmail.com

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ABSTRACT

Helminths are parasitic worms that can infect humans. They are broadly classified as flatworms (including Cestodes and Trematodes) and roundworms (nematodes). These worms infect organs such as intestines, liver, skin, as well as other tissues. These infections are more common in underdeveloped parts of the world affecting almost one-sixth of the world population. These infections can lead to a variety of endocrine manifestations. A decreased risk of developing type 2 diabetes mellitus has been observed in affected populations. Helminths modulate the host immunity towards a type 2 immune response which is anti-inflammatory in nature. An increase in T regulatory cells has also been seen which reduces T cell response to infections. By virtue of these changes, chronic inflammation is suppressed in adipose tissues - this phenomenon may explain the protective effect in type 2 diabetes mellitus. A reduction in insulin resistance independent of BMI has been observed in animal as well as human studies. Hepatic lipid production can be reduced by the soluble egg antigen from certain schistosomes. The immunomodulatory effects of helminth infections can also protect against autoimmune endocrine conditions such as type 1 diabetes mellitus and Graves' disease. These observations may reflect the well-known "hygiene hypothesis". Thyroid nodules and hypothyroidism can occur in helminth infections. Insights into thyroid physiology, including thyroid hormone receptors and de-iodination pathways, have been obtained from studies in helminths. Certain helminth infections can impair osteoclast maturation suggesting potential implications for osteoporosis. Similarities between human and helminth bone morphogenetic protein pathways have been observed. Adrenal masses as well as adrenal insufficiency, have been observed in helminth infections. Infertility has frequently been reported with Schistosomiasis due to inflammation in the genital tracts. An estrogen like compound may be produced by schistosomes which can lead to hypogonadism in males. The helminth, Caenorhabditis elegans can serve as a model for studies on Kallman syndrome as the KAL-1 gene appears to be functionally conserved in this helminth. A reduction in IGF-1 levels may be seen in adults infected with helminths. Apart from these manifestations, novel insights regarding endocrine disease mechanisms as well endocrine physiology can be derived from studies on helminths.

INTRODUCTION

The term helminth refers to parasitic worms which are broadly classified as flatworms (including Cestodes and Trematodes) and roundworms (nematodes) (1). These infections may be soil-transmitted and present as intestinal infections while others may invade different tissues such as blood vessels or other organs. These parasitic worms are endemic in several parts of the world, specifically in underdeveloped and parts of developing countries (1). It is estimated that approximately one-sixth of the world's population is affected by helminth infections (2). Helminths employ complex mechanisms to evade host immunity. They induce malnutrition in the host while simultaneously ensuring an adequate supply of nutrients for their own growth and reproduction.

Table 1. Classification of Helminths

PHYLUM	Affected Organ	Examples
Platyhelminths	Intestine	Cestodes -Taenia, Echinococcus
	Liver	Trematodes- Schistosoma, Fasciola
	Intestine	Ascaris, Enterobius, Necator, Ancylostoma,

Nematodes		Trichuris, Strongyloides
	Cutaneous	Strongyloides
	Tissues	Onchocerca, Loa, Wuchereria

These immunological and metabolic interactions between helminth and the host may modulate the pathophysiology of several endocrine disorders including diabetes, thyroid disorders, and gonadal disorders apart from others. A discussion of each of these groups of disorders is presented below.

DIABETES MELLITUS

Diabetes mellitus is among the most common endocrine disorders with its rapidly growing prevalence earning it the designation of a pandemic. While type 1 diabetes mellitus is an autoimmune disease, type 2 diabetes is mediated by insulin resistance which is of multifactorial origin with genetics, environmental factors, and inflammation all playing their part. Among these factors, it has been noticed that areas with a high prevalence of soil-transmitted helminth infections have a relatively lower prevalence of diabetes (3). Although several other factors may also be operational in such areas, there are several proposed mechanisms by which helminth infections may influence diabetes and its pathogenesis.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus has been described as a chronic inflammatory disorder. Chronic inflammation in adipose tissues has been shown to be among the factors underlying this disease. The inflammatory process in adipose tissue involves infiltration by inflammatory cells such as lymphocytes, macrophages, and neutrophils. Eosinophils on the other hand appear to have an anti-inflammatory effect. Apart from infiltration, several phenotypic changes occur in these cells which tip the balance towards inflammation. These include the predominance of T helper type 1 (Th1) and T helper type 17 (Th17) instead of the T helper type 2 (Th2) and the regulatory T cells (Tregs). The Th1 and Th17 cells promote the macrophage activation into classically activated macrophages (CAM) which in turn secrete inflammatory markers such as tumor necrosis factor-alpha (TNF-α), interleukin 6 and 12(IL6, IL12). TNF-α has been shown to interfere with insulin signaling. On the other hand, Th2 and T reg cells secrete IL-3 and IL 4 which stimulate the formation of alternatively activated macrophages (AAM) which are anti-inflammatory and express IL-10. Adipokines such as leptin, lipocalin 2, retinol-binding protein (RBP4), resistin, angiopoietin-like protein 2 (ANGPTL2), IL-6, IL-1, CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5) are also pro-inflammatory while adiponectin may have anti-inflammatory actions.

Helminth infections are associated with induction of type 2 immune response which involves increased activation of Th2 cells, eosinophilia, and production of IgE. The Th2 response in turn manifests as increased secretion of IL-4, IL-5, IL-9, IL-10, IL-13 which are anti-inflammatory. This also promotes the induction of anti-inflammatory AAMs. Similarly, helminth infections are associated with an increase in T reg cells which mediate a state of T cell hypo-responsiveness. These changes on one hand limit the damage to host tissues by uncontrolled inflammation in response to helminth antigens and on the other hand prevent the clearance of the helminth from the host. The T cell hypo-responsiveness to parasite antigens can spill over to other antigens as well and this phenomenon has been invoked to explain the reduced prevalence of certain allergic and autoimmune disorders in helminth infected populations. Therefore, it has been hypothesized that since the immunological changes associated with helminth infections are anti-inflammatory in nature, they can reduce chronic inflammation in adipose and other tissues, thereby mitigating insulin resistance and the resultant type 2 diabetes.

The above hypothesis is supported by epidemiological data. In a study from China, previous schistosome infection was associated with a lower prevalence of obesity and metabolic syndrome as compared to those without such infection (4). Another study, which used ultrasonography to document chronic liver disease caused by schistosomiasis, found that metabolic syndrome prevalence was reduced to half of that seen in those without evidence of schistosomiasis (5). Serological evidence of chronic Strongyloides stercoralis infection was associated with a 61% lower risk of developing type 2 diabetes as compared to those who did not have this infection, despite adjustment for parameters such as age, BMI, and hypertension (6). In Indonesia, higher insulin sensitivity was demonstrated in patients who had infections with soil-transmitted helminths as evidenced by lower BMI and HOMA-IR levels (7). A randomized controlled trial to demonstrate the effect of ongoing helminth infection on insulin sensitivity has been conducted (8). This trial randomized households in an area endemic for helminth infection to receive albendazole or placebo over a period of time. In this trial, treatment of helminth infected subjects with albendazole lead to an increase in insulin resistance along with a reduction in IgE

and eosinophil counts. However, at the community level, insulin resistance remained unchanged (9).

While the mechanisms of the reduction in type 2 diabetes have not been concretely studied in humans, animal studies provide support for the role of immunomodulation. Infections with Schistosoma mansoni, Nippostrongylus brasiliensis, and Litomosoides sigmodontis have been shown to increase eosinophils and AAMs in mice with diet-induced obesity (10–12). These animals had improved insulin sensitivity and glucose tolerance - this effect was lost in eosinophil deficient mice. S. mansoni soluble egg antigen and egg-derived ω-1 antigens stimulate innate lymphoid type 2 cells which produce IL-5 and IL-13 cytokines necessary for sustaining eosinophils and AAMs (13). L. sigmodontis Ag-treated obese mice had greater numbers of CD4+Foxp3+ Tregs in white adipose tissues as compared to controls indicating the upregulation of these cells as a mechanism of reducing insulin resistance (12).

Apart from these immunomodulatory mechanisms, the effect on body weight and gut microbiota are also potential mechanisms. The soluble egg antigen of S. japonicum, has been shown to reduce hepatic expression of microRNA 802 (miR802) which suppresses hepatic lipid production by upregulating the AMPK pathway. This has been proposed to be a future therapeutic target in obesity (14). However, the effect of helminth infection on insulin sensitivity has been shown to be independent of BMI in mice (10). This echoes the study on Australian aboriginals where the findings persisted despite adjusting for BMI (6).

Similarly, data on gut microbiota changes is scanty and conflicting. A few studies show an increase in gut bacterial diversity after helminth infection (15,16). Other authors have not found any significant changes in gut microbiota (17). While the mechanisms require further elucidation in both animal as well as human studies, there seems to be sufficient evidence to support the role of helminth infections in modulating the pathophysiology of type 2 diabetes.

Type 1 Diabetes Mellitus

Regarding type 1 diabetes, the type 2 immune response and suppressive regulatory environment induced by helminths may induce a protective effect. The incidence of type 1 diabetes has been increasing rapidly in developed countries and these regions are relatively less affected by helminth infections (18). The hygiene hypothesis has been invoked to explain this phenomenon (19). There are very few human studies which directly look at helminth infection and amelioration of type 1 diabetes risk. Enterobiasis did not reduce risk of type 1 diabetes in a population based study (19). Several animal studies do support the protective role of helminth infection. Axenic Caenorhabditis elegans antigen can protect against type 1 diabetes in the non-obese diabetes (NOD) mouse model (20). Trehalose produced by some helminths can alter intestinal microbiota leading to induction of CD8+ T cells which protect against type 1 diabetes in mice models (21). The severity of type 1 diabetes in mice models is ameliorated by recombinant Schistosoma japonicum cystatin and fructose-1,6-bisphosphate aldolase (22). Interestingly, children with schistosomiasis appear to have islet cell antibodies and defects in insulin secretion when compared to non infected siblings of children with insulin-dependent diabetes mellitus (23). Future studies may further shed light on this interesting topic.

THYROID DISORDERS

There appears to be a bidirectional relationship between the thyroid gland and helminth infections. On one hand, helminths appear to possess several proteins which are analogous to those involved in human thyroid physiology while on the other hand helminths can play a role in several thyroid diseases.

Thyroid hormone receptors which were earlier thought to be found only in chordates have been found to be present in S. mansoni (24). Two homologues of mammalian thyroid receptor (TR) has been isolated and characterized in S. mansoni (25), The thyroid hormone receptor beta from S. japonicum has also been characterized and evaluated as a vaccine candidate for this infection (26). Similarly, a nuclear hormone receptor has been identified in S. stercoralis which has some resemblance with steroid/thyroid hormone receptor found in humans (27). A transthyretin like protein has also been identified in Schistosoma dublin and Caenorhabditis elegans, although its function is unclear (28). Thyroid hormones may be essential for helminth growth and multiplication. In mice infected with Schistosoma mansoni, thyroid hormone therapy led to parasite multiplication and an increase in size whereas iodine deficient or thyroid hormone receptor knockout mice had lesser parasite numbers and smaller sized worms (29).

Some novel insights into thyroid physiology have also come from studies in helminths. Studies on the nematode Caenorhabditis have helped elucidate the mechanisms behind toxic effects of excess iodine - the dual oxidase maturation factor (DOXA-1) being among the implicated factors (30). Similarly, helminth studies have shown that iodotyrosine deiodinase may also have a role in regulating potassium channels in muscles (31).

Hypothyroidism and Thyroid Nodules

With respect to thyroid disorders, hypothyroidism and thyroid nodules appear to have some associations with helminth infections. S. stercoralis has been associated with hypothyroidism in one case report (32). Fasciola gigantica infection in buffaloes has been shown to lead to lymphocytic thyroiditis and hypothyroidism (33).

Hydatid cyst disease can mimic thyroid nodules and is often diagnosed by fine needle aspiration cytology (34). Cysticerosis may also present as a thyroid nodule (35). Similarly, microfilaria have also been found in fine needle aspirations from the thyroid (36). Schistosomiasis may interfere with technetium pertechnetate uptake in various tissues including the thyroid as demonstrated in mice- this may have implications for thyroid scan performed in infected humans (37).

Hyperthyroidism

Graves' disease, which is the most common cause of hyperthyroidism, may be affected by helminth infections. Considering that helminths affect host immune response and Graves' disease is an autoimmune process, such an association is not unexpected. Graves' disease is characterized by autoantibodies to the TSH receptor which leads to gland enlargement, hyperthyroidism, as well as extrathyroidal manifestations such as orbitopathy and dermopathy. Animal models of Graves' disease have been developed which involve introduction of TSH receptor complementary DNA. It has been shown in such a mouse model that prior infection with S. mansoni may lead to a sustained Th2 type immune response towards the parasite egg antigens. This Th2 type immune response prevented the development of Graves' disease when mice were immunized with non-replicative recombinant adenovirus expressing the human TSHR. However, if given after disease onset, the Schistosoma infection could not cure the disease. Graves' disease was once thought to be a Th2-type immune response, but recent studies have described a Th1-type as well as a Th2-type response suggesting that reversal of an activated immune response to the TSH receptor is not possible (38). Based on similar findings with other infections, a hygiene hypothesis for Graves disease has also been proposed (39).

BONES AND CALCIUM METABOLISM

There is limited information regarding calcium metabolism and bone health in helminth infections. Hydatid cyst disease involving the vertebrae has been described recently and pathological hip fracture has also been reported (40,41). However, this is likely to represent direct involvement of the bone rather than alterations in bone metabolism.

Inflammatory arthritis is associated with secondary osteoporosis. The Th2 type immune response seen with helminth infections may attenuate inflammatory arthritis. N. brasiliensis was able to inhibit arthritis and bone loss in two experimental models of inflammatory arthritis (42). In vitro osteoclast differentiation has been shown to be inhibited by excretory/ secretory products from Heligmosomoides polygyrus bakeri, a murine helminth (43). C-terminal sequence of Fasciola helminth defense molecule-1 (C-FhHDM-1) has been shown to reduce RANKL secretion as well as prevents both the formation of osteoclasts and acidification of lysosomes in animal models [6]. These features may be beneficial in osteoporotic states. However, in a study on pregnant mice, Heligmosomoides bakeri infection in late pregnancy and lactation led to a decrease in maternal bone mineral density and was associated with an increase in levels of inflammatory cytokines (IL-1 beta and IL-6) (44).

There may be several similarities between human and helminth physiology with respect to certain metabolic pathways. Homologues of osteonectin, also called SPARC [Secreted Protein Acidic and Rich in Cysteine]), have been found in C. elegans while S. mansoni has homologues of TGF-beta receptor (45,46). More recently, it has been found that bone morphogenetic protein signaling may be conserved between humans and helminths, especially C. elegans. Secreted Modular Calcium-binding protein-1 (SMOC-1) gene identified in Caenorhabditis elegans may promote BMP signaling leading to the growth of the helminth (47,48). While BMP pathway plays several roles in human physiology including bone growth, the implications of these discoveries in helminths are still unclear.

ADRENALS

Helminth infections in the adrenal with presentation as an adrenal mass have been reported in the literature. Paragonimus westermani has been reported in a patient who had a lung cavity and an adrenal mass (49). Echinococcus multilocularis can infrequently present as a right adrenal mass detected incidentally (50). Adrenal schistosomiasis has also been reported (51). F. gigantica can cause adrenal insufficiency in animals (33). Acute adrenal insufficiency accompanied by adrenal hemorrhage has also been reported with S. stercoralis (52).

Activation of the hypothalamic-pituitary-adrenal axis leading to immunosuppression has been shown in mouse studies with Angiostrongylus cantonensis (53). While chronic immunosuppressive therapy can lead to hyperinfection with helminths like S. stercoralis (54,55), adrenalectomized mice appeared to have higher worm

burden and worm fecundity rates when infected with S mansoni (56). Previous mouse studies have shown adrenal hypertrophy and higher cortisol levels in S. mansoni infection (57). In vitro treatment of S. mansoni with adrenal hormones suggests that DHEA has a toxic effect with cercariae being more susceptible than schistosomula and adults (58).

GONADS

The manifestations of helminth infections with respect to gonads include hypogonadism and infertility.

Hypogonadism

S. mansoni infection has been associated with low normal testosterone and elevated estrogen levels in males although hepatic dysfunction may also play a role in these abnormalities (59). Patients infected with Loa loa and Mansonella perstans filariasis are more likely to have low testosterone and elevated gonadotropins as compared to control subjects (60). Further research in this area revealed that an estradiol-related compound was present in schistosome worm extracts (61). Later, the same authors confirmed the presence of this estradiol-related compound by mass spectrometry and also demonstrated that this compound has an antagonistic activity on the estrogen receptor and leads to a reduced expression of the estrogen receptor (62). Schistosome eggs can also convert estrogens to catechol-estrogens which in turn can be metabolized to active quinones. These quinones can cause DNA modifications and are implicated in the pathogenesis of malignancies related to schistosomiasis (63). These hormonal changes explain the pathogenesis of hypogonadism in schistosomiasis.

Infertility

Schistosomiasis has been well recognized as a cause of infertility especially in females. Apart from hypogonadism caused by alterations in the estrogen axis, schistosomiasis can affect the genital tract leading to infertility. Genital involvement occurs in the form of granulomatous inflammation, fibrosis, and adhesion formation. The manifestations of this infection in females include tubal blockage, tubal pregnancy, tubal abortions, hemoperitoneum, preterm births, and miscarriages (64). Males can also have direct testicular inflammation along with, blockage of the genital ductal system and venous drainage leading to infarction. However, the involvement of male genital tract has been reported infrequently (65). Female infertility has also been reported with enterobiasis (66). Filarial involvement of male genitalia leading to hydrocele is well recognized (67). Male sterility can occur in such cases (68).

Some insights into genetic hypogonadism may come from helminth studies. The gene responsible for Kallman syndrome, KAL-1, appears to have a functionally conserved homologue in C. elegans. This gene plays a role in morphogenesis by influencing migration of epidermal cells in C. elegans. This discovery has established C. elegans as a model for study of Kallman syndrome for which a mouse model has proved to be elusive [33].

GROWTH

Children with helminth infections may have impaired growth- a phenomenon that can easily be attributed to malnutrition. However, helminth infections in adults are associated with significantly lower free IGF-1 which showed improvement after anti-helminth treatment(69). IGF-BP3 levels remain unchanged. Thus, direct effects on the GH-IGF-1 axis may occur in these infections.

CONCLUSION

Table 2. Endocrine Manifestations of Helminth Infections
May protect against development of type 2 and type 1 diabetes mellitus
Hypothyroidism and thyroid nodules
May protect against Graves' disease
May protect against osteoporosis
Adrenal masses and acute adrenal insufficiency
Hypogonadism and infertility
Growth failure via reduction in IGF-1levels

In conclusion, helminths appear to play an important role in several endocrine disorders in endemic areas. Apart from contributing to the pathogenesis of disease, they may have a protective effect in some metabolic disorders. Novel insights regarding endocrine disease mechanisms as well endocrine physiology can be derived from studies using helminths. This is an interesting area for research

which should encourage both helminthologists as well as endocrinologists.

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