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Helminth Infections and Diabetes: Mechanisms Accounting for Risk Amelioration

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Abstract

The global prevalence of type 2 diabetes mellitus (T2D) is increasing rapidly, with an anticipated 600 million cases by 2035. While infectious diseases such as helminth infections have decreased due to improved sanitation and health care, recent research suggests a link between helminth infections and T2D, with helminths such as *Schistosoma*, *Nippostrongylus*, *Strongyloides*, and *Heligmosomoides* potentially mitigating or slowing down T2D progression in human and animal models. Helminth infections enhance host immunity by promoting interactions between innate and adaptive immune systems. In T2D, type 1 immune responses are suppressed and type 2 responses are augmented, expanding regulatory T cells and innate immune cells, particularly type 2 immune cells and macrophages. This article reviews recent research shedding light on the favorable effects of helminth infections on T2D. The potential defense mechanisms identified include heightened insulin sensitivity and reduced inflammation. The synthesis of findings from studies investigating parasitic helminths and their derivatives underscores promising avenues for defense against T2D.

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INTRODUCTION

Diabetes, a complex spectrum of metabolic disorders characterized by improper or inadequate insulin production, has emerged as a significant global health concern. With an alarming prevalence, it affects an estimated 537 million individuals worldwide. Projections indicate a worrisome trajectory, with expectations that this number will escalate to 643 million by 2030 and a staggering 783 million by 2045. The implications of diabetes extend beyond the sheer numbers, as evidenced by the anticipated 6.7 million fatalities attributed to the condition in the year 2021 alone (56).

Type 2 diabetes mellitus (T2D) stands out as a prominent subtype within the diabetes spectrum. Characterized by chronic inflammation and persistent elevation of blood glucose levels due to insulin resistance, T2D has become a major contributor to global morbidity and mortality (55, 69, 76, 92). Effective management of T2D and its associated complications involves a multifaceted approach, encompassing lifestyle modifications such as the right diet and exercise, alongside pharmacological interventions (19). As the prevalence of T2D continues to rise, understanding its complexities and implementing targeted interventions become paramount in mitigating the global burden of this chronic inflammatory illness.

While traditionally considered a metabolic condition, there is growing recognition of the intricate interplay between T2D and the immune system, highlighting the role of immunology in the development and progression of the disease (6). T2D is associated with chronic low-grade inflammation, a state in which the immune system is chronically activated. This inflammatory environment is believed to contribute to insulin resistance and the impairment of pancreatic β cell function, key factors in T2D development (84). Adipose tissue (fat) is not just a storage depot; it is also an active endocrine organ that releases various signaling molecules (84). In T2D, there is an infiltration of immune cells, particularly macrophages, into adipose tissue. In T2D, there is an imbalance in cytokine production, with an increase in proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (4). These cytokines can interfere with insulin signaling and contribute to insulin resistance. There is evidence to suggest that autoimmunity may also play a role in some cases of T2D (4). Autoimmune responses against β cells can contribute to β cell dysfunction and impaired insulin secretion (84). The gut microbiota, comprising trillions

of microorganisms in the digestive tract, has been linked to both metabolic and immune functions. Alterations in the gut microbiota composition have been observed in individuals with T2D, and this dysbiosis may contribute to systemic inflammation and insulin resistance (113).

Helminth infections represent a significant public health concern, impacting more than 1.5 billion individuals globally, constituting 24% of the population (38, 39). The enduring coevolution of helminths with humans, as posited by evolutionary theory, has yielded mutual benefits for both host and parasite. The seminal 1989 hygiene hypothesis publication by Strachan (93) generated interest in the potential of helminth infections to mitigate human diseases. Despite successful eradication efforts reducing helminth-related incidence rates and mortality, a consequential rise in the prevalence of Western disorders such as T2D has been observed (31).

T2D caused by obesity and metabolic syndrome (MetS) is more common in well-developed urban areas with low worm burdens (103). Helminth infections have been shown to improve symptoms, control food intake, and reduce body weight. Widespread malnutrition negatively impacts immunity, especially cellular immunity. The shift toward Western diets, characterized by excessive calorie intake, increased consumption of highly processed foods, and reduced intake of fruits and vegetables, may lead to deficiencies in at-risk groups (35). Epidemiological research indicates that obesity, associated with inflammation and increased fat deposition, is correlated with reduced bacterial diversity. Conversely, helminth infection has been linked to higher bacterial richness and may confer benefits for obesity (85).

The primary mechanism contributing to insulin resistance and T2D in obese individuals is inflammation occurring in adipose tissue. Obesity-related dysfunction in adipose tissue exposes individuals to risks such as T2D, hypertension, and kidney and cardiovascular disorders (104). Interestingly, under obesity-related conditions, the activation of the host immunological response to T2D seems to have a dual function in promoting adipose tissue homeostasis and adapting to stress (48, 63, 68).

The extensive coadaptation history between helminths and humans is evident in the prevalence and chronicity of helminth infections (22). Early-life exposure to helminths contributes to the development of self-tolerance and the preservation of immunological balance, ultimately lowering the prevalence of inflammatory disorders such as diabetes (26). Helminth parasites, known for migrating and feeding on host tissues, induce significant tissue damage. In response, mammalian hosts have evolved a regulatory immune response phenotype aimed at encapsulating the parasites and facilitating tissue repair (27). Notably, endemic helminth infections exhibit an inverse correlation with the incidence of inflammatory disorders, with industrialized nations experiencing higher rates of dysregulated immune responses and associated diseases (110). Long-lived helminths establish themselves in various organs, modulating the host's immune system, metabolite synthesis, and nutrient flow to facilitate their adaptation on the basis of their requirements (61). However, the host organism strives to counteract immunological and metabolic changes induced by this coexistence and mitigate potential harm (68).

The typical immune response to helminth parasite infection involves the establishment of a robust anti-inflammatory, type 2 immune response, differing from the proinflammatory T helper type 1 (Th1) response mounted against micropathogens. T cells secrete IL-4, IL-5, and IL-13 during this response, while macrophages are polarized toward an anti-inflammatory M2 phenotype, suppressing M1 inflammatory macrophages and inhibiting proinflammatory Th1 and Th17 responses (1, 5, 71, 102). This immune polarization aims to encourage tissue regeneration and establish a regulatory network for long-term parasite survival (12, 21).

Numerous epidemiological and experimental studies, including those by Hübner et al. (40), Aravindhan et al. (4), Chen et al. (13), Hussaarts et al. (41), and Rajamanickam et al. (77, 78, 80, 81), have documented the positive effects of helminth infections on T2D. Given the intimate

connection between T2D inflammation and helminth infections, particularly those derived from helminth products, novel treatment options may emerge to prevent or treat diabetes. This discourse delves into the potential advantages of helminth infections and the administration of helminth-derived compounds for T2D, as well as the potential underlying protective mechanisms.

EPIDEMIOLOGICAL INSIGHTS: HELMINTH INFECTIONS AND THE INVERSE ASSOCIATION WITH DIABETES RISK

Epidemiological evidence strongly supports an association between helminth infections and a reduced risk of diabetes, indicating an inverse correlation between helminth prevalence and diabetes incidence and implying a potential protective effect (21, 111). Direct evidence from various epidemiological studies establishes an inverse link between helminths and diabetes (4, 13, 33, 60, 64, 89, 102). Metabolic disease factors such as the prevalence of MetS and T2D, as measured by homeostatic model assessment of insulin resistance (HOMA-IR), have been reported to associate with exposure to helminth infections (13, 33, 89). Intriguingly, several studies consistently found an inverse correlation between metabolic diseases and both recent and past helminth infections (4, 13, 33, 60, 64, 89, 102). These studies, conducted in diverse regions including Turkey, China, Brazil, India, Australia, and Indonesia, investigated various helminth species, encompassing soil-transmitted helminths, filariae, and schistosomes (4, 13, 33, 60, 64, 77, 78, 80, 81, 89, 102). Notably, diabetic groups consistently exhibited fewer intestinal parasites than control groups (64). A study by de Ruiter et al. (21) revealed no overlap in the percentage of children requiring preventative chemotherapy for soil-transmitted helminths in various nations.

In regions with a high prevalence of both helminth infections and diabetes, such as remote areas, *Strongyloides stercoralis* infection was associated with a significantly decreased incidence of T2D (33). Similarly, a strongly negative correlation between lymphatic filariasis incidence and T2D was observed in Asian Indians with both conditions, suggesting a decreased proinflammatory immune response (4, 77). Chen et al. (13) reported a significantly lower prevalence of T2D in individuals with a history of schistosomiasis compared with those without the condition.

Additionally, individuals with prior *Schistosoma* infection were less likely to have MetS and exhibited reduced body mass indexes; lower levels of plasma fasting blood glucose, postprandial blood glucose, and glycated hemoglobin A1c (HbA1c); and lower HOMA-IR scores (89). A meta-analysis and other aforementioned studies collectively indicate that individuals with past or present helminth infections are 50% less likely to experience hyperglycemia, T2D, MetS, or insulin resistance than those without infection (98). These findings suggest that persistent helminth infections may exert a long-lasting impact on the emergence of metabolic disorders. Moreover, PrayGod et al. (75) observed a connection between geohelminth and *Schistosoma* infections and decreased β cell activity in human immunodeficiency virus (HIV)-positive individuals not receiving antiretroviral therapy. Interestingly, *Schistosoma* infection was associated with increased β cell function in HIV-uninfected individuals.

Infection with human hookworm *Necator americanus* is safe, well tolerated, and associated with Th2 and regulatory T cell responses, making it a potential treatment for inflammation associated with MetS and T2D (16, 28, 44, 73, 74). In Australia, a double-blind clinical trial explored the safety of hookworm infection for adults at risk of T2D, revealing potential metabolic benefits. The study demonstrated that hookworm-treated groups experienced reductions in fasting glucose levels and insulin resistance after one year, and body mass was decreased after two years of hookworm treatment (74). These findings collectively suggest that helminth infections may play a positive role in T2D, potentially contributing to delaying the onset of T2D and mitigating associated pathological effects.

While some epidemiological studies have consistently demonstrated an inverse association between helminth infections and diabetes, challenges (4, 13, 33, 60, 64, 89, 102) and contradictory evidence (34, 39, 59, 87, 108) exist. A recent investigation conducted in northern Thailand revealed an inverse correlation between *S. stercoralis* infection and T2D. However, individuals infected with *S. stercoralis* exhibited higher urine albumin-to-creatinine ratios and alanine aminotransferase levels, along with lower estimated glomerular filtration rates. This suggests that renal biochemical markers associated with complications may worsen due to *S. stercoralis* infection (108).

This discrepancy underscores the complexity of the relationship, suggesting that factors such as host genetics, helminth species, and regional variations may contribute to divergent outcomes. Moreover, the lack of uniformity in study methodologies and diagnostic criteria for diabetes and variations in helminth species prevalence across populations pose challenges to drawing definitive conclusions (51). The heterogeneity in these studies emphasizes the need for more standardized approaches and larger sample sizes to better elucidate the nuances of the helminth–diabetes association (51). Despite the accumulating epidemiological evidence, a striking gap exists in the form of limited clinical trials specifically designed to investigate the interaction between helminth infections and diabetes. Clinical trials provide a rigorous platform for assessing causality and elucidating mechanistic insights, yet their scarcity in this context hinders a comprehensive understanding of the relationship. The lack of clinical trials is partly attributed to ethical considerations and concerns about deliberately infecting individuals with helminths. However, innovative trial designs, such as those leveraging naturally acquired infections in endemic regions, could offer valuable insights.

EXPLORING THE THERAPEUTIC INTERFACE: HELMINTH MODULATION OF TYPE 2 DIABETES IN ANIMAL MODELS

Helminths, having coevolved with vertebrate hosts, exhibit the ability to modulate the immune system toward an anti-inflammatory state, potentially offering avenues for treating and preventing the effects of T2D. An array of animal models is currently employed to study T2D, including the high-fat diet (HFD)-induced obesity model, MetS model, ob/ob mouse model, *Lepr*$^{db/db}$ mouse model, and RIP2-OPa1-deficient mouse model (26).

In murine models, infection with *Schistosoma mansoni*, as well as immunization and exposure to helminth products, has been observed to enhance Th2 immune responses in adipose tissues. This enhancement correlates with improved insulin sensitivity, glucose tolerance, and overall metabolic status (41, 54, 96). Additionally, *Schistosoma japonicum* soluble egg antigens (SEAs) have demonstrated the ability to reduce insulin resistance by elevating regulatory T cells (Tregs) and Th2 cytokines (95). Immunization with specific SEA components, such as Lewis^X-containing lacto-*N*-fucopentaose III, has shown promise in enhancing insulin sensitivity and glucose tolerance in obese mice by upregulating IL-10 expression in alternatively activated macrophages (AAMs) and dendritic cells (DCs) (8, 99).

Mice infected with *Strongyloides venezuelensis* exhibited improvements in insulin signaling and sensitivity, accompanied by a shift from M1 to M2 macrophages in adipose tissues, influenced by alterations in gut microbiota (70). *Heligmosomoides polygyrus* infection in mice has been associated with lower weight gain, reduced glucose intolerance, and improved lipid profiles (65, 90), leading to decreased blood glucose levels, fat accumulation, and HOMA-IR scores and downregulation of *FAS* gene expression in the liver (62). Su et al. (94) demonstrated that *H. polygyrus* infection operates via a M2 macrophage-dependent mechanism. Mice infected with *Trichinella spiralis* displayed reduced body weight gain, fat mass, and total cholesterol and alterations in iron transporters, indicating a potential role in metabolic regulation (43). Products derived from *Acanthocheilonema*

viteae were found to enhance metabolic function (52). Infection with *Nippostrongylus brasiliensis* in mice has been associated with improved insulin sensitivity and glucose tolerance (106, 107).

This exploration of helminth interactions in various murine models underscores the potential therapeutic impact of helminths on T2D, presenting a promising avenue for further research and clinical consideration.

EXPLORING THE INTERPLAY: HELMINTH INFECTIONS AND TYPE 2 DIABETES IN HUMAN STUDIES

T2D is a prevalent metabolic condition that exhibits an increasing frequency from late adolescence into midlife (30). As per International Diabetes Federation estimates in 2021, the prevalence of diabetes exhibits an age-related increase. Projections for 2045 indicate a continuation of this trend. In 2021, adults aged 20 to 24 showed the lowest prevalence at 2.2%. Notably, individuals in the age group of 75–79 years had a prevalence of 24.0%, expected to rise to 24.7% by 2045. The global demographic shift toward an aging population contributes to a higher percentage of individuals with diabetes aged 60 years and above (56). Notably, studies have revealed a significant reduction in the prevalence of helminth infections among T2D patients compared with nondiabetic controls, suggesting a potential protective effect of T2D against helminth infections (13, 33). Helminth infections, by modulating host immune responses, have been proposed to confer protection against the development or exacerbation of T2D (92). *S. stercoralis*–infected individuals exhibit substantial alterations in glycemic, hormonal, and cytokine parameters related to T2D (77), and these alterations are reversible with anthelmintic treatment (77). Individuals with filariasis, *S. stercoralis*, and hookworm infections demonstrate significantly decreased insulin and glucagon levels compared with uninfected individuals (20, 77, 81). It has been proposed that helminths and their products may employ an adiponectin-mediated mechanism to mitigate adipose tissue T cell inflammation, a phenomenon that increases significantly following anthelminthic therapy (77). Furthermore, adults with *S. stercoralis* infection have been shown to exhibit the potential to protect against the development of T2D-associated pathology by reducing pathogenic cytokine and chemokine levels (78).

Aravindhan et al. (4) observed higher levels of ghrelin, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) in filarial-positive individuals compared with filarial-uninfected individuals, consistent with findings in obese individuals infected with *S. stercoralis* (4, 78, 81) and T2D individuals with hookworm infections (20). Additionally, individuals with *S. stercoralis* infection exhibited higher adiponectin levels and lower resistin, visfatin, leptin, and plasminogen activator inhibitor 1 (PAI-1) levels (81). Visfatin and incretin levels, on the other hand, were much higher in *S. stercoralis*–infected persons than in *S. stercoralis*–uninfected individuals. Remarkably, after anthelmintic treatment, this impact did not manifest. Likewise, individuals with both hookworm infection and T2D exhibited significantly lower levels of random blood glucose and HbA1c compared with those with T2D alone. Moreover, the hookworm-infected individuals with T2D demonstrated notably reduced concentrations of glucagon, insulin, C-peptide, adiponectin, and adipsin in comparison with subjects with T2D alone. Visfatin and incretin levels were significantly higher in individuals with hookworm infections compared with uninfected individuals. Interestingly, this effect did not manifest after anthelmintic treatment (20). The impact of helminth infection on T2D is illustrated in **Figure 1**.

In diabetic individuals, elevated Th1 cytokine levels and decreased Th2 cytokine levels are commonly observed. Notably, in lean individuals, AAMs within adipose tissue contribute to reduced inflammation and enhanced insulin sensitivity through processes mediated by IL-10 and regulatory T cells (66). Chronic helminth infections induce a modified Th2 immune response,

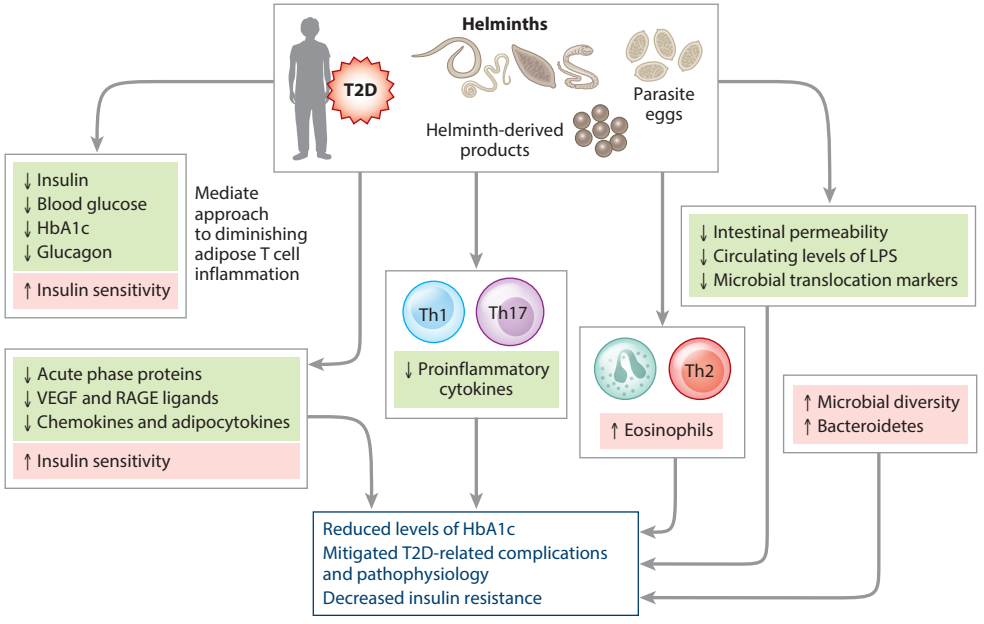

Figure 1

Influence of helminth infection on type 2 diabetes mellitus (T2D). This schematic representation illustrates the beneficial impact of helminth-induced systemic immune responses on T2D, highlighting mechanisms that potentially prevent or delay T2D-related pathogenesis. Research findings indicate that individuals coinfected with helminths and T2D demonstrate reduced levels of glycometabolic parameters, markers of microbial translocation, circulating lipopolysaccharide (LPS), acute phase proteins, ligands for receptor for advanced glycation end products (RAGE) and vascular endothelial growth factor (VEGF), intestinal permeability, T helper type 1 (Th1) and Th17 cytokines, and proinflammatory cytokines and chemokines. Conversely, elevated levels of total immunoglobulin E, Th2 cytokines, microbial diversity, and Bacteroidetes are observed. These alterations collectively contribute to heightened insulin sensitivity and lowered hemoglobin A1c (HbA1c) levels, ultimately mitigating T2D-related complications and pathophysiology.

promoting parasite survival and diminishing host immunity (18, 33). The nature of the helminth infection may contribute to the interaction with T2D, with diabetic individuals potentially having fewer well-adapted chronic infections characterized by a reduced Th2 reaction compared with nondiabetic individuals (33).

Significantly, individuals with T2D displayed a decreased percentage of filarial antigen-specific immunoglobulin G4 (IgG4) titer. TNF-α and IL-6 levels are lower in T2D and *Wuchereria bancrofti* patients compared with those with T2D alone (4, 18). In individuals with T2D and *S. stercoralis* infection, there was a notable decrease in levels of angiogenic factors, including vascular endothelial growth factor A (VEGF-A), VEGF-C, VEGF-D, angiopoietin 1 (Ang-1), and Ang-2, as well as their soluble receptors (VEGF-R1, -R2, and -R3). Additionally, levels of advanced glycation end product (AGE) ligands, soluble receptors for advanced glycation end product (sRAGE), S100 calcium-binding protein A12 (S100A12), and high-mobility group box 1 (HMGB-1) were decreased in individuals with T2D and *Strongyloides* infection compared with those without helminth infection. Interestingly, after anthelmintic medication, there was an increase in angiogenic factors and sRAGE ligands, suggesting that *Strongyloides* infection might offer benefits by preventing or delaying vascular problems associated with T2D (80).

This data overview sheds light on the intricate relationship between helminth infections and T2D in human studies, emphasizing the multifaceted impact of helminths on the metabolic landscape.

IMMUNOLOGICAL MECHANISMS UNDERLYING THE PROTECTIVE INFLUENCE OF HELMINTH INFECTIONS AGAINST TYPE 2 DIABETES

Research has consistently demonstrated that helminth infections influence key processes related to T2D, such as insulin resistance, blood glucose levels, HbA1c levels, and dyslipidemias (4, 13, 33, 77, 102). Proinflammatory cytokines and chemokines associated with T2D are suppressed by helminth infections, contributing to reduced systemic inflammation (3, 4, 77, 78, 102). Cross-sectional studies indicate that prior helminth infection may confer immune-mediated protection against T2D through the induction of a chronic, low-grade, Th2/Treg-mediated immune suppression (41).

Filarial antigens derived from helminths induce immune responses, including IL-10 production by DCs and B lymphocytes, activation of AAMs, and modulation of Toll-like receptor signaling (36, 41, 100). Recent research findings propose that diabetes conditions contribute to heightened Th9 polarization and increased expression of various cytokines and factors, including IL-27, IL-1Ra, IL-12, IL-33, IL-9, stromal cell-derived factor 1 (SDF-1), cyclooxygenase 2 (Cox-2), and indoleamine 2,3 dioxygenase (IDO). Interestingly, these factors can be influenced by helminth infections to mitigate chronic pathology, as observed in individuals with lymphatic filariasis (91).

The IL-4/STAT6 (signal transducer and activator of transcription 6) axis, integral to helminth immunity and allergies, has been identified as a regulator of insulin sensitivity and peripheral nutrient metabolism (83). Experimental studies have shown that insulin sensitivity improves with Th2 polarization induced by IL-4 administration, highlighting the crucial role of eosinophils, which secrete IL-4, in maintaining glucose homeostasis and sustaining AAMs in white adipose tissue (11, 53, 106). The immune axis of IL-4/STAT6 has been linked to improved insulin sensitivity in HFD-fed mice, emphasizing its potential therapeutic relevance in T2D (21, 83).

Studies on various helminths, such as *S. mansoni*, *S. venezuelensis*, *N. brasiliensis*, and *T. spiralis*, in T2D mouse models suggest that helminth infections contribute to the recruitment of M2-like macrophages in adipose tissue, leading to a reduction in chronic proinflammatory responses associated with obesity and improved insulin resistance (7, 41, 107). Helminth-mediated macrophage modulation, evident in various T2D mouse models, may play a pivotal role in preventing T2D by alleviating inflammation in adipose tissue and positively affecting β cell function (7).

Helminths possess the ability to decrease energy intake, potentially enhancing insulin sensitivity directly through calorie restriction and indirectly via Th2 activation. A prior investigation revealed that IL-33, produced by islet mesenchymal cells and influenced by diabetes, plays a role in promoting β cell function through islet-resident group 2 innate lymphoid cells (ILC2s). This axis, activated following acute β cell stress, becomes impaired during chronic obesity. IL-33 injections demonstrated the potential to restore islet function in obese mice, highlighting an immunometabolic cross talk involving islet-derived IL-33, ILC2s, and myeloid cells (17).

In animal studies, the impact of helminths on lipid homeostasis may be elucidated by various underlying mechanisms, including (*a*) parasitism of host dietary nutrients, utilizing lipid resources for their survival and reproduction; (*b*) modification of gut microbiota and intestinal lipid metabolism; and (*c*) immune-dependent or -independent regulation of lipid metabolism in immune cells and/or peripheral tissues by helminths and their molecules (114). The observed

reduction in serum lipid levels in individuals infected with *Schistosoma haematobium* might be attributed, at least partially, to increased metabolism of fatty acids and cholesterol by different immune cells circulating in the bloodstream and/or residing in tissues due to helminth-induced host immunomodulation, as demonstrated, for instance, in the liver macrophages of infected mice (15, 114).

In summary, the comprehensive understanding of the immunological mechanisms orchestrated by helminth infections provides valuable insights into their potential as therapeutic agents in preventing or ameliorating T2D. These multifaceted effects, encompassing cytokine modulation and immune cell regulation, underscore the intricate interplay between helminths and the immune-metabolic axis in the context of T2D. The potential protective mechanism of helminth infection against T2D is illustrated in **Figure 2**.

Helminths can directly impact immune regulatory function through the secretion of various products and may indirectly modulate immune responses by influencing the composition of the intestinal microbiota (73). For instance, in mice, infection with gastrointestinal helminths prevented

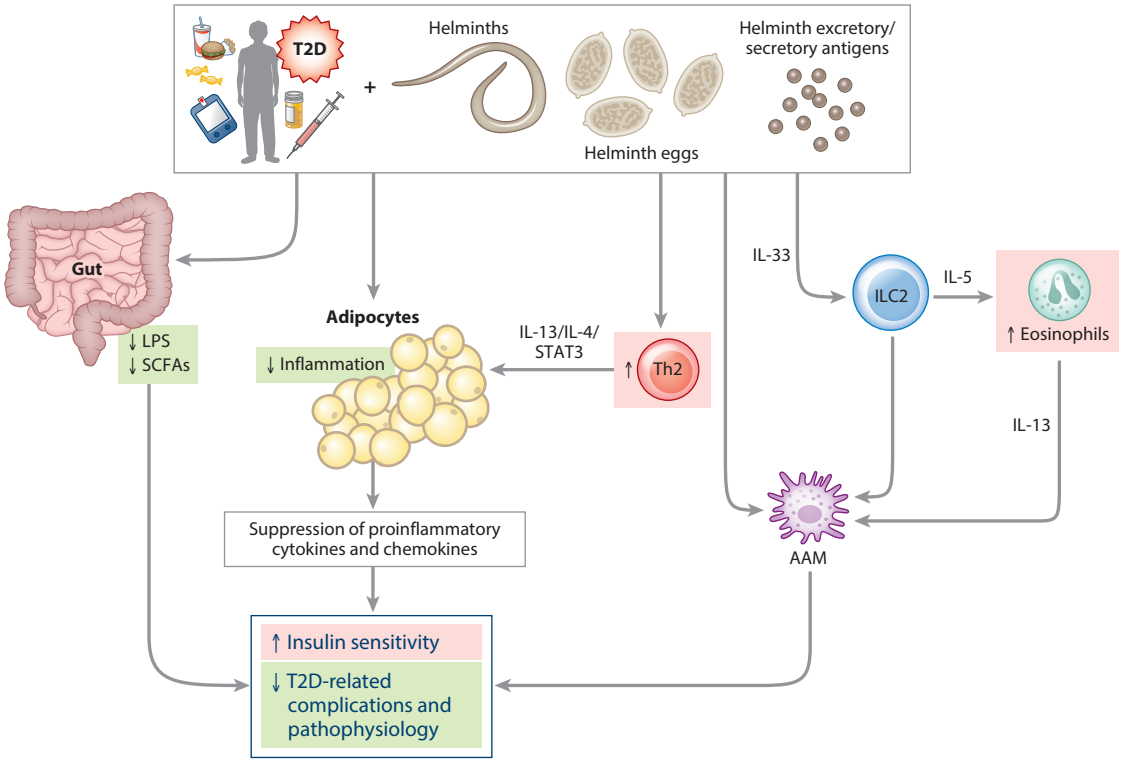

Figure 2

Potential protective mechanisms of helminth infection in type 2 diabetes mellitus (T2D). This figure illustrates the potential protective mechanisms underlying the impact of helminth infection or helminth-derived products on T2D homeostasis. Helminth infections or their compounds exhibit the capacity to mitigate T2D and associated complications by reducing metabolic inflammation and promoting adipose tissue browning. Within adipose tissues, helminth infections induce the proliferation of T helper type 2 (Th2) cells and eosinophils, leading to the polarization of M2 phenotype macrophages. This, in turn, triggers the release of anti-inflammatory cytokines such as interleukin 5 (IL-5) and IL-13, contributing to the alleviation of gut microbiota dysbiosis. Key components involved in these processes include lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), group 2 innate lymphoid cells (ILC2s), signal transducer and activator of transcription 3 (STAT3), and alternatively activated macrophages (AAMs).

colonization with the proinflammatory bacterium *Bacteroides vulgatus* (82). Another mechanism involves the induction of eosinophil buildup in the mesenteric lymph nodes, adipose tissue, liver, and small intestine, along with increased expression of genes encoding important Th2 cytokines and M2 macrophages in adipose tissue, liver, and small intestine. This helminth-induced response promotes type 2 immune responses (45). The regulation of eosinophils in bone marrow is primarily controlled by IL-5, and their recruitment into white adipose tissue is influenced by local and systemic increases in eosinophils, Th2 cytokines, and M2 macrophage numbers. The precise mechanism underlying the regulation of obesity-induced insulin resistance and adipose tissue inflammation is not yet clear, but it may involve direct effects of eosinophils on insulin resistance or secondary effects on body weight and adiposity (45).

EXPLORING THE IMPACT OF HELMINTH INFECTIONS ON GUT MICROBIOTA: IMPLICATIONS FOR TYPE 2 DIABETES

Understanding the complex interconnection between gut microbiota, metabolic processes, and immune responses is crucial, particularly in the context of T2D. Extensive studies on the human microbiome highlight the pivotal role of gut microbiota in metabolic and immune response processes associated with T2D (50, 109). Digestive factors such as GLP-1, GIP, and short-chain fatty acids directly interact with pancreatic β cells, influencing their proliferation and resistance to apoptosis, thus impacting β cell mass and metabolic function (57, 58). Adding a layer to this intricate relationship, helminth infections have been shown to influence gut microbiota composition, leading to alterations in the functional characteristics of macrophages and impacting insulin sensitivity (2, 10, 25). The potential protective effect of helminth infections against T2D involves modulating the gut microbiota, thereby affecting metabolic responses.

Alterations in gut microbiota can impact intestinal permeability, contributing to microbial translocation and metabolic endotoxemia associated with T2D (9, 49). Studies reveal that helminth infections may mitigate metabolic endotoxemia in a diabetic environment, possibly through the differential interaction between the infection and gut microbiota (79). Chronic helminth infection acts as an immunomodulator, dampening metabolic endotoxemia in T2D. Elevations in acute phase proteins and microbial translocation markers are common in chronic inflammation associated with metabolic disorders, including T2D (29, 72). The association between helminth infections and a protective impact on intestinal dysbiosis, metabolic endotoxemia, and systemic inflammatory milieu provides valuable insights into the potential benefits in the context of T2D (79).

T2D is commonly associated with systemic inflammation and microbial translocation, considered pivotal factors in T2D-associated pathology (23, 97). Helminth infections contribute to modulating the systemic inflammation observed in T2D by suppressing proinflammatory cytokines and chemokines (77, 78). Our research has demonstrated a reduction in metabolic endotoxemia [lipopolysaccharide (LPS), soluble CD14, LPS binding protein, and endotoxin IgG antibody] and intestinal permeability (intestinal fatty acid binding protein) in the presence of *S. stercoralis* infection (79). While *Strongyloides* infection promotes microbial translocation, its impact in a diabetic environment is downmodulated due to the intricate interplay between helminth infection and the gut microbiota (79).

Chronic inflammation, a hallmark of metabolic disorders such as T2D, is often characterized by elevated acute phase proteins. Unresolved endoplasmic reticulum stress and oxidative stress play pivotal roles in instigating inflammatory responses in metabolic dysregulation. Inflammatory markers, particularly C-reactive protein (CRP), have been extensively associated with an increased susceptibility to T2D and cardiovascular diseases. A comprehensive meta-analysis incorporating

22 studies revealed a heightened risk of T2D and predicted cardiovascular events with elevated CRP levels. Furthermore, markers such as alpha 2-macroglobulin (α-2M), serum amyloid protein A1 (SAA1), and haptoglobin, linked to diabetic complications and disease duration, suggest that reducing these proteins might mitigate the occurrence of complications in T2D. In the context of T2D, helminth infection has been correlated with microbial translocation and a concurrent reduction in systemic inflammation. Markers of systemic inflammation (levels of acute phase proteins) and microbial translocation (levels of LPS and its associated products) were examined in individuals with T2D and *Strongyloides* infection. Additionally, these parameters were analyzed at 6 months following anthelmintic treatment. Significantly diminished levels of α-2M, CRP, haptoglobin, and SAA1 were observed in *Strongyloides*-infected individuals compared with uninfected individuals. These levels increased significantly following therapy (79). The impact of helminth infection on T2D is illustrated in **Figure 1**.

The above studies underscore the intricate relationship between helminth infections and gut microbiota and their collective impact on T2D. Further elucidation of the molecular processes underlying the protective effect of helminth infections opens avenues for understanding and potentially harnessing these interactions for therapeutic purposes in the realm of T2D.

EXPLORING THE LINK BETWEEN HELMINTH INFECTIONS, NUTRITION, AND TYPE 2 DIABETES

Crucial for the developing immune system, nutrients are often lacking in regions with helminth infections, which are compounded by malnutrition and bacterial coinfections (86). Deficits in vitamins and minerals worsen parasitic infections, with urban areas having low worm burdens facing a higher incidence of metabolic diseases such as obesity-induced T2D and MetS (103). Helminth infection regulates food intake, appetite, and body weight, showing potential benefits for MetS and T2D symptoms. Parasitic nematodes impact cellular metabolism directly or indirectly through gene activation, influencing the gastrointestinal tract and host nutritional status (88).

Malnutrition has been a historical challenge, affecting immunity, particularly cellular immunity (88). Children with malnutrition show reduced gut barrier function, lymphatic tissue atrophy, and a Th2-polarized cytokine response, yet this does not necessarily improve resistance to nematode infections. Reduced protein content in diets delays primary infection expulsion, while protein malnutrition decreases tolerance to infection by affecting intestinal barrier function (42, 46). Western diets, with excessive caloric intake and reduced nutrients, pose risks, affecting at-risk populations in the 20th and 21st centuries (101). Micronutrients such as vitamin A, selenium, and zinc are crucial for immune function and parasitic infection resistance (88).

Obesity affects type 2 immune responses, with obesity-prone mouse strains being more susceptible to parasitic nematode infection (105). Obesity induces chronic inflammation (metaflammation) and insulin resistance, involving both immune and nonimmune cells (37). Immunometabolism investigates proinflammatory cytokines in obesity, MetS, and T2D. Parasitic infections elevate IL-4, IL-5, and IL-13, potentially reversing Th1-induced inflammation (67).

Vitamin D is crucial for pancreatic β cell function and MetS (14). Vitamin D deficiency reduces oxidative stress, inflammation, and insulin secretion (32). Mineral deficiencies disrupt glucose homeostasis and insulin resistance (24). Magnesium, a glucose access cofactor, may alleviate insulin resistance in hypomagnesemia (47). Zinc, essential for insulin, regulates islet cell secretion and reduces reactive oxygen species formation (112).

In summary, malnutrition and bacterial coinfections in developing areas contribute to chronic helminth infection, which is exacerbated by deficiencies in vital nutrients. Urban areas with low worm burdens face higher rates of metabolic diseases, and malnutrition impacts immunity and

resistance to parasitic infections. Obesity influences type 2 immune responses, causing chronic inflammation and insulin resistance.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite the limited number of epidemiological studies exploring the relationship between helminth infections and T2D, consistent findings suggest a potential protective role of helminths against T2D development. This observed association remains robust across diverse populations and various helminth species, emphasizing its potential significance. However, the reliance on cross-sectional methodologies underscores the need for longitudinal studies to establish a causal link between helminths and T2D.

An alternative avenue, garnering significant interest, involves investigating helminth treatment as a strategy to enhance metabolic outcomes. Clinical studies treating patients with inflammatory conditions, including Crohn's disease, ulcerative colitis, celiac disease, asthma, and multiple sclerosis, with helminths have yielded equivocal outcomes. The temporal aspect of helminth-induced immunomodulatory effects remains unknown, posing challenges in managing existing inflammatory reactions compared with preventing their onset. Early infections may crucially influence the development of the immune regulation network, with a potential impact on the regulatory network's tolerance in endemic regions.

Helminth parasites intricately control interactions among islet macrophages, β cells, and other endocrine cells, constructing an environment conducive to retaining β cell mass and function. This suggests a promising avenue for a potential cure for T2D by leveraging the survival methods of helminths in mammalian hosts. Notably, experimental helminth infections or the incorporation of helminth-derived compounds in diet-induced obese mice have demonstrated enhanced glucose tolerance and increased insulin sensitivity compared with controls. These insulin-sensitizing effects are attributed to alterations in immune cell composition induced by helminths, particularly in white adipose tissue. To validate this helminth-associated change in immune cell composition toward a regulatory, anti-inflammatory milieu and understand its implications for whole-body insulin sensitivity, in-depth immunological investigations in human subjects are imperative.

In regions with widespread helminth infections, dietary interventions become sensible, considering the influence of nutrition on an individual's resistance to such infections. Therapeutic approaches utilizing helminth products may also benefit from proper nutrition. Moreover, helminth infections significantly impact host metabolism, particularly energy metabolism, suggesting the potential for innovative methods in treating conditions such as T2D and obesity.

In conclusion, evidence from animal models and cross-sectional epidemiological studies supports the notion that helminth infections may exert a preventive influence against the onset of T2D. Unraveling the proteins governing these immunomodulatory effects holds the potential to usher in novel therapeutic approaches for T2D management.

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