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Review

Immunological and Pathophysiological Outcomes of Helminth Infections and Type 2 Diabetes Comorbidity Studies in Humans and Experimental Animals—A Scoping Review

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Abstract: Animal and human studies have demonstrated that helminth infections are associated with a decreased prevalence of type 2 diabetes mellitus (T2DM). Lack of exposure to helminth infections has been postulated to be one mechanism to explain the markedly increased prevalence of T2DM in developed countries. However, there is still paucity of information regarding the immunological interactions between helminth infections and T2DM. The study aimed at reviewing peer-reviewed articles on host immune and pathophysiological outcomes from human and laboratory animal studies of helminth infections and T2DM comorbidity. A literature search was carried out in Google Scholar, PubMed, and EBSCOhost databases using the following keywords; immune responses OR immune modulation of helminth infections OR parasites infections AND Type 2 diabetes comorbidity in humans AND experimental/laboratory animals. Results showed that helminth infections provided some degree of protection from the pathology associated with T2DM by modulating the surrounding cytokine and chemokine milieu in humans and animals. Whilst there is some evidence regarding the protective effects of helminth infections to T2DM in cases of comorbidity, there is paucity of research in both laboratory animals and humans, with reference to the immunological and pathophysiological mechanisms which occur during comorbidity, and these constitute gaps for future research.

Keywords: comorbidity; type 2 diabetes mellitus; helminths; infection outcomes; immune response; humans and laboratory studies

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic inflammatory disease that is characterized by constant increase in glucose levels due to insulin resistance (IR), and is associated with the infiltration of macrophages and T cells into adipose tissue and an elevation in the production of pro-inflammatory cytokines (Th1 and Th17) [1,2]. When β cells are destroyed in the pancreas, secretion of insulin is negatively affected leading to diabetes [3]. It has now developed to be a global world health problem, contributing significantly to morbidity and mortality worldwide [4,5]. According to estimation, about 415 million people of the world's total population are currently living with T2DM, and the number is estimated to reach 642 million by 2040 [6]. Type 2 diabetes mellitus accounts for over 90–95% of all diabetic recorded cases [4] and modified lifestyles such as lack of or reduced physical activity, unhealthy eating habits and urbanization favor the development of T2DM [4]. This occurrence is not just in the developed countries, but also increasing at an alarming rate in developing countries [7]. Epidemiological studies have shown a significant increase in the prevalence of T2DM globally with India having the highest prevalence [7].

Approximately, more than 1.5 billion people are infected with one or more species of helminths, which is about 24% of the world's population [6]. There is an increase in the prevalence of comorbid cases of T2DM and helminthic infections and these may be associated with environmental and genetical factors [8]. The immunological interactions instigated by helminth infections to their hosts has been reported to polarize the immune system towards a strong type-2 immune response that is associated with immune defense and tissue repair [4].

Helminth infections affect close to one-quarter of the global population and are most prevalent in the lower and middle-income countries [8]. Experimental evidence and epidemiological studies have shown that helminths may play a protective role against the development of T2DM [9,10]. This has been attributed to low systemic inflammation propelled by the immune modulation, which is observed in chronic helminth infections [2]. In most cases, multi-morbidity in diabetic patients exacerbates the patient's condition and complicates the treatment strategy, therefore, affecting the success of the treatment. A previous study by Berbudi et al. [11] reported that the reduction in helminth infections through mass drug administration or other means in developing countries might contribute to the increase in the incidences of diabetes and other metabolic disorders; however, there is a paucity of reported literature or studies that bring a clearer view on the overall interaction of diabetes-helminths comorbidity in helminth endemic areas.

Helminths are known to be manipulators of host immune system and have the capability of inducing modified T-helper cells, type 2 (Th2) weighted immune responses, which also have the dual effect of reducing harmful inflammation in the host while ensuring the survival of the parasites [12]. More so, T2DM causes inflammation in adipose tissue in particular both a cause and consequence of insulin resistance in peripheral tissues [13,14]. On the other hand, helminth infections have been known to either exacerbate or ameliorate the occurrence of autoimmune responses in animal and human studies [15]. Helminths-induced type 2 immune responses are characterized by eosinophilia, high level of IgE, and increases in T-cell production of Interleukin-4, IL-5, and IL-13 and it has also been proven that IL-4 can directly reduce ongoing Th1-driven autoimmune inflammation [7]. Helminth infection also influences the production of the anti-inflammatory cytokines such as IL-10 and Transforming growth factor beta (TGF-β) and may result in the protective effect against diabetes onset [7].

Generally, helminths seem to protect the onset of type 1 DM, which is an autoimmune disease [16]. Several studies have reported relations between helminth infection and the prevention of onset of type 1 DM [15,16]. However, there are limited reports with reference to comorbidity of helminthiasis and T2DM. An earlier study by Daniele et al. [17] demonstrated that a low-grade chronic inflammation characterized by alterations in circulating immune-modulatory factors is linked with the pathogenesis of T2DM. However, Wu et al. [1] indicated that helminth infections ameliorate diet-induced insulin resistance by an immune-modulation. Considering the high global prevalence of helminth infections and the increasing prevalence of T2DM, it is important to understand the immunological and physio-pathological mechanisms which occur in the host during comorbidity of helminths and T2DM. Therefore, the present study is a scoping review on host immune responses outcomes from human and experimental animal studies comorbid with helminth infections and T2DM.

2. Materials and Methods

The scoping review framework as described by Arksey and O'Malley [18] was followed in the following order (a) identification of the research question; (b) identification of relevant articles; (c) selection of articles; (d) data charting; and (e) summarizing of results.

2.1. Identification of the Research Question

The scoping review was aimed at addressing the question, "what is known about immune responses of helminth infections and T2DM comorbidity in human and experimental

animal studies". A comprehensive approach was adopted to search for peer-reviewed articles that reported specifically on T2DM and helminths comorbidity research in order to answer this question. The process followed was consistent with the approach of a scoping review, which is to synthesize what is known about a particular matter across various literature forms in order to achieve clarity about the state of knowledge and evidence that exists.

2.2. Literature Search Strategy

A literature search was conducted using Google Scholar, PubMed, and EBSCO host databases to identify studies published from 2000 to 2020 (Figure 1). The literature search was aimed at identifying and reviewing humans and experimental laboratory animal-based studies involving helminth infections and T2DM comorbidity. The following search terms were used with Boolean operators (OR, AND): "Immune responses OR immune modulation of helminth infections OR parasites infections AND type 2 diabetes comorbidity in humans AND experimental/laboratory animals". The literature identified were assessed independently by ES, SIN, SIT and SM for inclusion based on their titles and abstracts. All reference lists from relevant studies were visually scanned through with the aim to further identify additional articles that were not identified during electronic database search. Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines for conducting and reporting review was followed Moher et al. [19]. The procedure followed is shown in the PRISMA flow diagram (Figure 1). The literature search was concluded in June 2020 and the full-text articles that were retrieved were managed using EndNote reference manager version X7.7.1 (Clarivate Analytics, Philadelphia, PA, USA).

2.3. Study Selection

Articles were included if they were published between 2000 and 2020 in a peer-reviewed journal. Titles and abstracts were screened by ES, SIN, SIT and SM and articles that met the following inclusion criteria were considered eligible for the review; full-length peer-reviewed journal articles, written in English language, focused on human or animal studies on the immune responses or immune modulation of helminth infections and T2DM comorbidity and disease outcomes reported. Articles were excluded from the study if their focus was not on helminth infections and T2DM comorbidity in humans or experimental laboratory animals. The selection process is shown in a PRISMA flow diagram (Figure 1).

2.4. Charting the Data and Summarizing the Results

The following data were extracted from articles that fulfilled the above inclusion criteria: author(s) name, year of publication, objectives of the study, country where the study was carried out, type of study, experimental animal host if not human, gender, the sample size, species of parasites, the diagnostic method(s) used for helminth infection and T2DM and major findings of study.

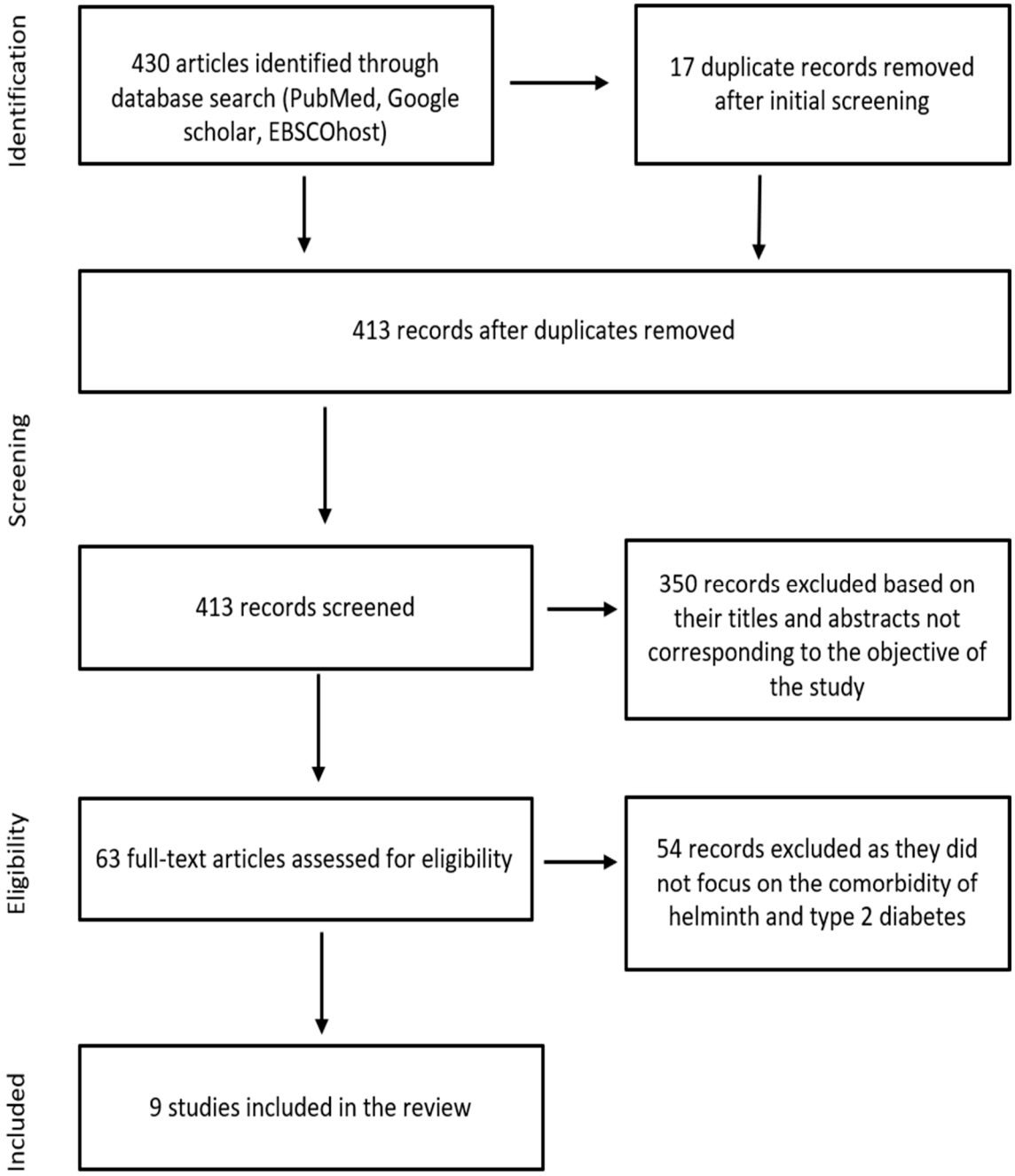

Figure 1. PRISMA diagram.

3. Results

3.1. Eligibility Search Results

Search results yielded 430 articles from three databases. Literature sought included peer-reviewed publications, reports and books, as shown in Figure 1. Initial screening led to the exclusion of 17 duplicates. After reading the titles and abstracts, 350 articles were deemed ineligible as the titles and/or abstracts were not relevant to the objectives of the study. Sixty-three articles were selected for full-text reading of which 54 articles were removed as their focus was not on comorbidity of helminths and T2DM of humans and experimental animals, leaving a total of nine articles being retained and included in this review. The remaining nine articles which were deemed eligible for inclusion were grouped into two categories: The first category was three articles focusing on animal studies on

helminths infection and T2DM comorbidity (Table 1) and the second category was six articles on human studies on helminths infection and T2DM comorbidity (Table 2).

3.2. Animal Studies on Helminths Infection and T2DM Comorbidity

Details of the experimental animal studies on helminths infection and T2DM comorbidity are shown in Table 1. Sample size of the selected experimental animal studies ranged from 12 to 55, the species of helminths used include *Schistosoma mansoni*, *Heligmosomoides polygyrus* and *Syphacia muris*. Female and male mice, and male rats were the animal hosts used for these experiments. Studies were conducted in Egypt and Japan and different diagnostic methods used to detect helminth infection ranged from portal perfusion (*Schistosoma mansoni*), PCR (*Heligmosomoides polygyrus*) and cellophane tape method (*Syphacia muris*). Specimen type, such as liver, intestine, spleen, pancreas and eggs, were collected for determination of helminths infection and blood was collected for T2DM diagnosis (Table 3).

The results of the review are summarized in Table 1 as follows: (i) *S. mansoni* infection provided protection against streptozotocin-induced T-cell-mediated pancreatitis; (ii) *H. polygyrus* provided an effective option for the treatment of T2DM by improving inflammatory status through restoration of the cytokine imbalance, inhibition of glucose absorption from the small intestine and decline in excess fat accumulation in the liver; and (iii) significant reduction in blood glucose level in the *S. muris*-infected fa/fa rats when compared to that of control group.

3.3. Human Studies on Helminths Infection and T2DM Comorbidity

The sample size of the selected human studies ranged from 118 to 1463 and included both males and females. The studies were conducted in India (three studies) and Australia (three studies). Serum and fecal samples were collected to determine helminths infection. *Wuchereria bancrofti*, and *Strongyloides stercoralis* were the helminth species used in the human studies. A variety of diagnostic methods, such as *W. bancroffi* Og4C3 antigen capture (*W. bancrofti*), ELISA test (*S. stercoralis*), stool microscopy (*S. stercoralis*), multivalent PCR test (*S. stercoralis*) and Kato-Katz (*S. stercoralis*), were used to determine helminth infections. Kato-Katz technique is one of the methods used to detect soil-transmitted helminth eggs in fecal samples. Techniques used to determine T2DM were glucose oxidase and enzymatic technique (Table 3).

Studies showed reduced prevalence of *W. bancrofti* among diabetic subjects when compared to non-diabetic and pre-diabetic subjects. While *S. stercoralis* infection was reported to offer protection against the development of T2DM in humans through the immunomodulation mediated by excretory/secretory proteins. Additionally, *S. stercoralis* also provided a degree of protection against the severity of T2DM by modulating adipocytokines and the associated cytokine milieu. The results also indicate that *S. stercoralis* infection may provide a degree of protection from the pathology associated with T2DM by modulating the surrounding cytokine and chemokine milieu.

Table 1. Summary of animal studies on helminths infection and type 2 diabetes mellitus comorbidity and the outcomes of the study.

Reference	Study Objectives	Country	Animals (Number)	Animals (Model)	Helminth Species	Major Findings
[20]	To investigate the effect of schistosomiasis infection on glucose uptake by the diaphragm.	Egypt	55	Female Swiss albino mice	*Schistosoma mansoni*	i. Diabetic mice infected with *S. mansoni* showed a depressed glucose uptake by the diaphragm when compared to the control diabetic mice. ii. Decreased glycogen content in the skeletal muscle isolated from the diabetic mice was observed as compared to non-infected group. iii. Conclusion made was that chronic *S. mansoni* infection provides protection against streptozotocin induced T-cell mediated pancreatitis.
[21]	To investigate whether nematode infection can modulate T2DM pathology through cytokine regulation in a T2DM mouse model.	Japan	Not described (ND)	Male KK-Ay/TaJcl Mice	*Heligmosomoides polygyrus*	i. Parasite induced Th2 immune responses prevented type 2 diabetes in KK-Ay/TaJcl mice. ii. Eosinophils were mobilized in the submucosa of *H. polygyrus*-infected diabetic mice. iii. fat accumulation in the liver was observed in the *H. polygyrus* infected diabetic mice. iv. No difference in sodium glucose transporter (SGLT1) gene expression was observed in *H. polygyrus* infected diabetic mice.
[16]	To determine whether experimental infection with *Syphacia muris* delays the onset of hyperglycemia in fa/fa rats.	Japan	12	Male fa/fa rats	*Syphacia muris*	i. Significant decrease in blood glucose level was observed in the infected group when compared to that of control group. ii. *S. muris* infection also showed a delay in the onset of hyperglycemia in fa/fa rats. iii. *S. muris* infection did not have effect on the body weight, water and food intake or the organs of the rats that were examined. iv. Immuno-histochemical and histopathological examination of the pancreas showed traces of inflammation in both the *S. muris*-infected and the non-infected fa/fa rats.

Table 2. Summary of human studies on helminths infection and type 2 diabetes mellitus comorbidity and the outcomes of the study.

Reference	Study Objectives	Country	Population (N)	Gender	Helminths	Major Findings
[7]	To assess the baseline prevalence and the correlation of sero-positivity of *W. bancrofti* among diabetic subjects.	India	1463	Male/ Female	*Wuchereria bancrofti*	i. Decrease in prevalence of *W. bancrofti* was seen in subjects with type 2 diabetes, the decrease was associated with lower antigen load and anti-*W. bancrofti* IgG antibodies. ii. Low prevalence of *W. bancrofti* was also due to *W. bancrofti* -mediated mortality since *W. bancrofti* is known to be a chronic non-lethal disease. iii. *W. bancrofti* comorbidity with T2DM showed a decreased level of TNF-α and IL-6 cytokines which was already associated with insulin resistance. iv. In the comorbidity group of both *W. bancrofti* and T2DM, there was a reduction in the pro-inflammatory cytokines TNF-α and IL-6 when compared to the group without *W. bancrofti* suggesting the influence *W. bancrofti* has on the development of insulin resistance (IR).
[22]	To explore the relationship between infection with *Strongyloides stercoralis* and the likelihood of having type 2 diabetic mellitus.	Australia	259	Male/ Female	*Strongyloides stercoralis*	i. According to the result of this study, helminths infections resulted in an improved metabolic profile through immune-modulation process of helminth infections. ii. Significant increase in eosinophil count was observed among patients with T2DM when compared to those without. iii. Chronic *S. stercoralis* infection may, over time, protect against the development of T2DM. iv. Comorbidity of T2DM and *S. stercoralis* protects against the development of T2DM in humans.
[2]	To access the relationship between a soil transmitted helminth *Strongyloides stercoralis* and T2DM.	India	118	Male/ Female	*Strongyloides stercoralis*	i. *S. stercoralis* was associated with decrease in insulin and glucagon level which was reversed after treatment with anthelmintic. ii. There was no significant difference in resistin leptin and visfatin between the groups. iii. *S. stercoralis* provides a degree of protection against T2DM by modulating adipocytokines.

Table 2. *Cont.*

Reference	Study Objectives	Country	Population (N)	Gender	Helminths	Major Findings
[23]	To determine the effect of treatment for *S stercoralis* on type 2 diabetes mellitus in an Australian Aboriginal population.	Australia	259	Male/ Female	*Strongyloides stercoralis*	i. Treatment of *S. stercoralis* infection led to the reduction of intensity of inflammatory reaction which resulted in an improved glycemic control. ii. More pronounced weighted immune reaction with increased levels of Th2 inflammatory cytokines were observed in the diabetic group. iii. Persisting positivity to *S. stercoralis* may have effect in the reduction of cytokine production.
[24]	To explore the efficacy of ivermectin in the treatment of serological diagnosed cases of *S. stercoralis* infection in an Aboriginal community and to describe factors that may influence the outcome of treatment.	Australia	259	Male/ Female	*Strongyloides stercoralis*	i. The study showed that ivermectin is an effective treatment for *S. stercoralis* and that pre-existing T2DM might be a risk factor for treatment failure. ii. T2DM patients with relative infections of *S. stercoralis* have higher numbers of auto-infective larvae with subsequent re-establishment of a patent infection.
[25]	To examine the association of cytokines and chemokines in helminth-diabetes comorbidity.	India	118	Male/ Female	*Strongyloides stercoralis*	i. Co-existent chronic *S. stercoralis* infection is associated with a dampened inflammatory cytokine and chemokine response in T2DM. ii. The study demonstrated the depression of circulating levels of cytokines and chemokines in the *S. stercoralis* and T2DM comorbidity group. iii. A degree of protection was provided by *S. stercoralis* from the pathology associated with T2DM by modulating the levels of cytokines and chemokines milieu.

Table 3. Summary of the diagnostic techniques used in the helminth/type 2 diabetes mellitus comorbidity studies included in the review.

References	Country	Animal/ Human Host	Total Sample Size (N)	Type of Diabetes/Helminths		Samples Collected for Determination of Infection		Diagnostic Techniques Used		Outcome of T2DM and Helminth(s) Comorbidity Group		
				Diabetes	Helminths	Diabetes	Helminths	Helminths	Diabetes	Protection	No Change	No Protection
[20]	Egypt	Female Swiss albino mice	55	T2DM	*Schistosoma mansoni*	Blood	Liver/ Intestine	Portal perfusion	Glucose oxidase	+	-	-
[21]	Japan	Male KK-Ay/TaJcl mice	Not described (ND)	T2DM	*Heligmosomoides polygyrus*	Blood	Small intestine/Liver	PCR	Fuji Drichem System	+	-	-
[16]	Japan	Male fa/fa rats	12	T2DM	*Syphacia muris*	Blood	Eggs collected from the perianal region	Cellophane tape method	Glucose oxidase	+	-	-
[7]	India	Humans (male/ female)	1463	T2DM	*Wuchereria bancrofti*	Blood	Serum	*W. bancrofti* Og4C3 antigen capture	Glucose oxidase	+	-	-
[22]	Australia	Humans (male/ female)	259	T2DM	*Strongyloides stercoralis*	Blood	Not described (ND)	*S. stercoralis* ELISA test	Glucose oxidase	+	-	-
[2]	India	Humans (male/ female)	118	T2DM	*Strongyloides stercoralis*	Blood	Stool sample	Stool microscopy	Glucose oxidase	+	-	-
[23]	Australia	Humans (male/ female)	259	T2DM	*Strongyloides stercoralis*	Blood	Faeces	Multivalent PCR test	Glucose oxidase	+	-	-
[24]	Australia	Humans (male/ female)	259	T2DM	*Strongyloides stercoralis*	Blood	Not described (ND)	*S. stercoralis* ELISA test	Glucose oxidase	+	-	-
[25]	India	Humans (male/ female)	118	T2DM	*Strongyloides stercoralis*	Blood	Stool	Kato-Katz	Glucose oxidase	+	-	-

Key: -, no change; +, Protection.

4. Discussion

4.1. Outcomes of Helminths Infection and T2DM Comorbidity in Experimental Animal Studies

Type 2 diabetes mellitus is a chronic inflammatory metabolic disease which leads to chemokines and cytokines alterations, activation of different cell types and metabolic perturbations in different organs [2,26]. Clinical manifestations of T2DM are common in late adolescence and increase progressively into mid-life. Prevalence of inflammatory metabolic diseases such as T2DM are relatively high, especially in the developed countries [25]. Apart from this being a lifestyle disease associated with sedentarism, it might also be due to limited exposure to helminth infections which has been postulated as one mechanism to explain the markedly high prevalence of T2DM in developed countries [25,27]. Previous studies have demonstrated that the prevalence of helminth infections was remarkably reduced in T2DM individuals compared to non-diabetic controls, [22,28] thus, confirming a protective effect of T2DM against helminths infections. Both animal models and human studies have demonstrated that helminth infections can also protect against establishment or ameliorates T2DM [29]. These observations are further collaborated by Rajamanickam et al. [2], Shen et al. [9] and Tracey et al. [30], who concluded that helminth infections protect against T2DM by the alteration of host immune responses. A study by Rajamanickam et al. [2], demonstrated that alterations in the gut microbiota modulates glucose intolerance and adipose tissue inflammation. Additionally, there are reports that helminth infection alters the gut microbiome during obesity and also modulate glucose uptake, inflammation and insulin sensitivity [2,31], although the helminth infection and T2DM interface seems to be counter-regulatory with the effects of helminths on diabetic status still to be fully explored.

Findings from experimental animal studies have shown that chronic *S. mansoni* infection provides protection against streptozotocin-induced T-cell-mediated pancreatitis [20]. However, the protection did not provide better peripheral glycemic control, thus, modulation of cytokine production could be responsible for the observed decreased peripheral glucose uptake by the diaphragm [20]. Another study by Taira et al. [16] demonstrated that experimental infection with *S. muris* showed a delay on the onset of hyperglycemia in fa/fa rats. It was also suggested that inflammatory cytokine production may activate the onset of hyperglycemia in this model. According to Morimoto et al. [21], parasite-induced Th2 immune responses prevented T2DM in KK-Ay/Tajcl mice. Intraperitoneal glucose tolerance test (IPGTT) was significantly improved on *H. polygyrus* infection, suggesting that insulin sensitivity was recovered following *H. polygyrus* infection [21]. It has also been reported that the elevation of Th2 T-helper cells induces alternatively activated macrophages (AAMacs), which inhibit inflammation by producing IL-10. Th2 cytokines are associated with the promotion of IgE and eosinophilic responses in atopy, and interleukin-10 has more of an anti-inflammatory response [21,32]. AAMacs induction by Th2 T-helper cells might be one of the reasons underlying the improvement in the diabetic condition. Further studies still need to be reconsidered on the protective effect of helminth infection in T2DM, in order to devise therapeutic strategies for the treatment of autoimmune diseases. To define the role of each of the immune cells during the interaction of the immunity and metabolic systems, it would also be necessary to assess the effect of Th2, AAMac(M2) or eosinophil depletion. Future investigations are needed to understand the underlying mechanism of the delayed onset of T2DM in *S. muris* infected fa/fa rats, and other parasitic infections especially the tissue-dwelling parasites to determine whether the onset of hyperglycemia in fa/fa rats is delayed.

4.2. Outcomes of Helminths Infection and T2DM Comorbidity in Human Studies

According to Rajamanickam et al. [2] *S. stercoralis* infection was associated with decreased insulin and glucagon levels which was later reversed after treatment with an anthelmintic. The decrease in insulin could be as a result of pro- and anti-inflammatory adipokines imbalance. Adiponectin has been known to play a major role in the modulation of inflammation in different diseases [33]. It is also another mechanism by which helminths

infections influence glucose homeostasis and insulin resistance in T2DM [33]. Adiponectin is used in restraining the Th1 and Th17 cell glycolysis to mitigate inflammation and also unravels an adiponectin mediated mechanism that helminths and helminth-derived products may use to reduce adipose tissue T cell inflammation [2]. *Strongyloides stercoralis* infection has been reported to render a degree of protection against the severity of T2DM by the modulation of adipocytokines [2]. Another study by Hays et al. [24] demonstrated that *S. stercoralis* chronic infection can over time, offer protection against the development of T2DM through immune modulation.

Several studies have shown that the occurrence of T2DM is related to the overall level of inflammation presented over time [26]. Additionally, there are studies that have demonstrated a negative association between IL-10 and T2DM [34]. More so, the association between chronic inflammation in adipose tissue and the development of insulin resistance and T2DM has also been long established [2]. This inflammation is mediated through the Th1 immune response and "classically activated" macrophages, and it involves higher levels of pro-inflammatory cytokines such as TNF-α and IL-1b. Th1 cytokines produce the pro-inflammatory responses that is responsible for killing intracellular parasites and for perpetuating autoimmune responses. T helper type 1 (Th1) and Th2 responses was observed in diabetic patients where the level of Th1 cytokines was high, while the level of Th2 was reduced [35]. Additionally, in lean people, adipose tissue is infiltrated by alternatively activated macrophages (AAM) which causes reduction in inflammation and elevate insulin sensitivity through IL-10 and regulatory T cell-mediated process [36]. Chronic helminth infections induce a modified T-helper type 2 (Th2) immune response in the host mediated through a depletion in pro-inflammatory cytokines such as TNF-α and IFN-γ, and an elevation in anti-inflammatory cytokines such as IL-10 and TGF-ß, hence promoting the survival of the parasite and decreasing the risk of inflammatory injury in the host [22,37].

A study by Hays et al. [24] reported that the nature of the interaction between helminth infections and T2DM could be due to different kinds of helminth infections that are found in diabetic patients. It has also been established that worm numbers are likely to be higher in the early stage of infections and decrease to lower numbers during chronic infections [24]. Another study demonstrated that the helminth infections detected in T2DM patients were more likely to represent relatively recent infections contracted after the onset of T2DM. In contrast, the infections in non-diabetic patients were likely to represent well-adapted chronic infections with a modified Th2 reaction that is established in the host [22]. *Strongyloides stercoralis* infection provided a degree of protection from the pathology associated with T2DM by modulating the surrounding cytokine and chemokine [25]. Helminth infection significantly reduces the pro-inflammatory milieu in T2DM by decreasing the systemic levels of cytokines and chemokines, suggesting that helminth derived molecules or even helminth infection may offer a new therapeutic technique for treating inflammatory metabolic diseases [23,25]. Previous findings by Aravindhan et al. [7] reported that the prevalence of *W. bancrofti* among T2DM subjects was lower. This reduction in prevalence was associated with lower antigen load and anti-filarial IgG antibody titer but the anti-filarial IgG4 titer was not affected [7]. The decrease in IgG levels, and increased levels of IgA has also been previously reported [38]. T2DM and *W. bancrofti* comorbidity showed a decreased level of TNF-α and IL-6 compared to those with T2DM subjects alone [7]. The immune and non-immune mechanisms by which the interplay between *W. bancrofti* and T2DM occurs needs to be explored in detail. The effect of *S. stercoralis* infection on metabolic processes should be elucidated, and the protein(s) which are responsible for this effect identified. Further studies with *S. stercoralis* with larger numbers of patients and a longer time frame may be of interest, and a follow up for these individuals.

The primary limitation in the studies reviewed is the variation in the design and diagnostic techniques used, the moderate to low sample size and limited number of studies on helminths-T2DM comorbidity conducted in the last twenty years especially using animal models. Moreover, most of the studies reviewed did not provide a direct causative

mechanism for the decreased prevalence of glucose among diabetic subjects comorbid with helminth infections.

5. Conclusions

This review has revealed that helminth infections may provide a degree of protection for both humans and laboratory animals from the pathology associated with T2DM by modulating the surrounding cytokine and chemokine milieu. There is still paucity of information regarding the immunological interactions between helminth infections and T2DM during comorbidity, and this is a gap for future research including the immune and non-immune mechanisms by which the interplay occurs. Human cross-sectional studies have shown that chronic helminth infections in endemic regions of the world are associated with the induction of regulatory and anti-inflammatory networks, which may act to inhibit inflammatory responses, such as autoimmune, T2DM and allergic reactions. The potential for exploitation of this phenomenon has been considered in humans and laboratory animals for specific helminth species. However, maintaining healthy levels of helminths in the gut or tissue of the host for mutual benefits is still a challenge as critical gaps still remain such as the choice of helminth species and nature of infection in the human host.

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