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Research Article

Potential Association of *Strongyloides stercoralis* and its effectivity against Type 2 Diabetes Mellitus: A Systematic Review of Scientific Attestation

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ABSTRACT

The association of *Strongyloides stercoralis* in Type 2 Diabetes mellitus has put on a spotlight on various researchers after the discovery of *S. stercoralis*'s capability to conduct immunomodulation through lowering the production and release of cytokines, all of which provide a contradictory action towards the development of T2DM. T2DM results from a high number of macrophages that secrete cytokines and chemokines abnormally, which affects the B-pancreatic cells and leads to insulin resistance. However, regardless of this information, the linkage of the immunomodulation mechanism of *S. stercoralis* infection against T2DM still needs clarification and further validation. Thus, this systematic review was conceptualized to identify if there is a direct association between *S. stercoralis* and T2DM, including the effects of the helminth on patients with such a disease, and the underlying factors related to this relationship. Studies for the review were collected in the following databases: PubMed, ProQuest, Wiley, Open Access Theses and Dissertations (OATD), Internet Archive Scholars, and Elsevier. The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria was utilized to identify and screen eligible studies for review and among the chosen articles, three have suggested a direct association between *S. stercoralis* infection and T2DM, while two studies proved the absence of an association by statistical and clinical characteristics. These limited findings and conflicting evidence for a direct link between *S. stercoralis* and T2DM may indicate that the comorbidity of both factors points more toward an indirect relationship.

Keywords: *Helminth infection, Inflammatory disease, Insulin resistance, Strongyloides stercoralis, Type 2 Diabetes Mellitus*

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Introduction

With the increasing frequency of Type 2 Diabetes Mellitus (T2DM) and helminth infection all over the world, these two illnesses are regarded to be among the most significant global health diseases. The comorbidity of both diseases is also increasing, and various research has been conducted to investigate the link between helminth infection and T2DM. As a result, claims and arguments over the capacity of helminth infection, especially *Strongyloides stercoralis*, to protect against T2DM and other effects of these illnesses' comorbidity emerge. The researchers acknowledge the need to establish an association between these diseases and summarize the variables, comorbidity effects, and correlation between T2DM and *Strongyloides stercoralis* from a systematic review of the literature.

Methods

The Cochrane Handbook defines systematic review as a systematic search to discover all studies that match the eligibility criteria and an evaluation of the validity of the results of the included studies. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines for screening, evaluating, and synthesizing eligible studies [25].

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are used to identify, screen, and select studies included in the systematic review. The studies were categorized into two groups, those gathered via databases and registers and those gathered via other methods such as organizations and websites. The studies gathered were filtered and screened for eligibility, and those not meeting the inclusion criteria were excluded.

Materials and Instruments

In identifying, screening, and selecting the articles/journals for this study, the following order was followed: (a) identification of the research question; (b) identification of relevant articles; (c) selection of articles; (d) data charting and summarizing of results [26].

Inclusion and Exclusion Criteria

In this systematic review, the scientific articles and journals that were screened and reviewed must meet the following inclusion criteria to be considered eligible articles for review. Articles that did not meet the criteria were excluded from the study.

Table 1. Inclusion and Exclusion Criteria

CRITERIA	INCLUSION	EXCLUSION
Research Design	Quantitative studies	Other studies
Study topic	Relevant articles about the relationship between <i>S. stercoralis</i> and T2DM	Literature review that does not give details about the objectives of this study.
Population	Adults (>18Years old)	< 18 Years old
Effects Size	Studies with P value, correlational coefficient	Studies without P studies, correlational coefficient
Publication Type	full-length peer-reviewed journal articles	Non-peer-reviewed journal articles
Publication language	Mainly written in the English language	Written in other languages
Publication date	Year of publication from 2017 - present.	Articles published before 2017.

Eligibility Search Results

Following the identification, screening, and selection of studies using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the search results first yielded 227 articles, 200 of these came from four databases, namely, PubMed, ProQuest, Wiley, and Elsevier. The 27 remaining articles came from records identified via websites, organizations, and citation-searching methods. Initial screening led to the removal of 13 duplicates removed via EndNote X8. After reading the titles of the articles and the abstracts, 170 articles were deemed ineligible as they needed to meet the inclusion and exclusion criteria set fully, and the objectives were irrelevant to the study. Forty-three articles were selected for full-text reading, 36

from the databases and seven from the studies gathered via other methods. Out of the 36 articles from the three databases, 19 were removed as those articles contained a preliminary discussion on the relationship between *S. stercoralis* and T2DM (Reason 1), and an additional 13 were also removed due to its minimal discussion on the effects of *S. stercoralis* to patients with T2DM (Reason 2). On the other hand, out of the seven articles assessed for eligibility from gathered studies via other methods, six were removed for the same reason as Reason 1 from studies identified via databases. Five remaining articles were deemed eligible for inclusion and were then categorized according to *S. stercoralis* infection and type 2 diabetes mellitus comorbidity and the studies' outcomes (Table 2).

Table 2. Results on the summary of studies on *Strongyloides stercoralis* infection and type 2 diabetes mellitus comorbidity and the outcomes of the study

Reference	Title	Study Objectives	Country	Major Findings	The Outcome of T2DM and <i>S. stercoralis</i> Comorbidity Group	Relationship between T2DM and <i>S. stercoralis</i>	Factors present in accordance with the relationship of T2DM and <i>S. stercoralis</i>	Effect of <i>S. stercoralis</i> on T2DM patients
					Associated/ Not Associated	Direct/Indirect		
26	Imported <i>Strongyloides stercoralis</i> infection and diabetes mellitus and other metabolic diseases: Is there any association?	This study aims to evaluate the potential impact of strongyloidiasis in diabetes mellitus and other metabolic diseases.	Spain	When comparing patients with strongyloidiasis and uninfected patients, no differences were found regarding diabetes mellitus or other metabolic diseases.	Not associated	Indirect relationship	None	Although pathophysiological mechanisms support the idea that helminth infections may increase insulin sensitivity, in this cohort of patients, this did not find any association between <i>S. stercoralis</i> infection and type
15	Association of <i>Strongyloides stercoralis</i> infection and type 2 diabetes mellitus in northeastern Thailand: Impact on diabetic complication-related renal biochemical parameters	In this study, it aimed to investigate the relationship between <i>S. stercoralis</i> infection and T2DM in a rural area of Khon Kaen Province, Thailand.	Thailand	This finding indicates that <i>S. stercoralis</i> infection was inversely associated with T2DM.	Not associated	Indirect relationship	None	2 DM or other metabolic diseases. This study suggests that there is no association or effect of <i>S. stercoralis</i> infection to T2DM patients. As this did not find any significant differences in the levels of LDL-C, serum biochemical parameters (serum creatinine and uric acid) and BMI in both T2DM and non-T2DM with or without <i>S. stercoralis</i> infection.

27	Helminth infection modulates systemic pro-inflammatory cytokines and chemokines implicated in type 2 diabetes mellitus pathogenesis	To identify the association of cytokines and chemokines in helminth-diabetes co-morbidity and to prove that helminths are postulated to mediate a protective effect against T2DM.	India	Helminth infection significantly alleviates the pro-inflammatory milieu in T2DM by lowering the systemic levels of cytokines and chemokines	Associated	Direct relationship	With the diminished proinflammatory cytokines and chemokines such as –IL-1α, IL-1β, IL-6, IL-12, IL-18, IL-23, IL-27, G-CSF and GM-CSF and chemokines– CCL1, CCL2, CCL3, CCL11, CXCL1, CXCL2, CXCL8, CXCL9, CXCL10 and CXCL11 these hinder the formation of T2DM though preventing insulin resistance caused by these exaggerated pro-inflammatory cytokine and chemokine milieu.	<i>S. stercoralis</i> infection diminished the plasma levels of pro-inflammatory cytokines and chemokines in individuals with T2DM.
2	Metabolic Consequences of Concomitant <i>Strongyloides stercoralis</i> Infection in Patients With Type 2 Diabetes Mellitus	To assess the relationship between a soil-transmitted helminth, <i>Strongyloides stercoralis</i> (Ss), and T2DM	India	<i>Strongyloides stercoralis</i> infection is associated with a significant modulation of glycemic, hormonal, and cytokine parameters in T2DM and its reversal following anthelmintic therapy. Hence, Ss infection has a protective effect on diabetes-related parameters.	Associated	Direct relationship	The protective effect of <i>S. stercoralis</i> infection may provide a degree of protection against the severity of T2DM by modulating adipocytokines and the associated cytokine milieu	<i>S. stercoralis</i> infection may provide a degree of protection against the severity of T2DM by modulating adipocytokines and the associated cytokine milieu
28	The relationship between treatment for <i>Strongyloides stercoralis</i> infection and type 2 diabetes mellitus in an Australian aboriginal population: A three-year cohort study	The study aims to determine the treatment effect for <i>Strongyloides stercoralis</i> infection on type 2DM in the population of Australian Aboriginal	Australia	Participants who were treated for <i>Strongyloides</i> infection had an unadjusted 7.7 times higher probability of developing T2DM in the three years after treatment than an uninfected and untreated group. Despite a 3-year treatment, participants with a persistent	Associated	Direct relationship	Research showed that the eosinophilic penetration of adipose tissue could induce the generation of alternatively active macrophages, resulting in improved insulin sensitivity in the peripheral tissues through the production of anti-inflammatory cytokines (IL-10 and TGF), as well as the concomitantly decreased levels	The study discovered a significant improvement in the glycemic control improved more than the non-treated group. As a result, there is a discernible difference among community members who have had a prior infection successfully treated and those who have persistently positive ELISA results for <i>S. stercoralis</i> . This suggests that

positive result in ELISA to <i>S. stercoralis</i> had better glycemic control and lower TNF- and IL-10 production than those who responded to treatment. Positive ELISA for <i>S. stercoralis</i> has the potential for lowering the production of cytokine.	of pro-inflammatory cytokines.	persistent ELISA positivity for <i>S. stercoralis</i> may have some impact on reducing cytokine production.
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Discussion

Underlying factor(s) present in the relationship of Strongyloides stercoralis and T2DM

a. The Effects of the Decreased Levels of Pro inflammatory Cytokines and Chemokines

The abnormal elevation of macrophage levels and increased production of chemokines and cytokines are connected to the mechanism of T2DM genesis, per Meshkani et al.'s studies [29]. These cytokines and chemokines produced by macrophages can lead to localized or widespread inflammation, which impairs pancreatic beta-cell function. Adipose tissue, skeletal muscle, and the liver are just a few of the tissue types that may experience insulin resistance if beta cells, which produce insulin, are damaged.

In addition, three of the five studies that were selected for review came to the same conclusion that infection with *Strongyloides stercoralis* is associated with a reduction in several pro-inflammatory cytokines and chemokines. Rajamanickam et al. [27, 2] and Hays et al. [28] posit that these pro-inflammatory factors may play a role in the pathogenesis of T2DM. In particular, Rajamanickam et al.'s [2] study revealed a reduction in these factors in patients with both *S. stercoralis* infection and T2DM but not in patients with just one of these conditions.

In particular, the study published in 2020 by the same authors [27] noted that patients with *S. stercoralis* infection had lower levels of the chemokines CCL1, CCL2, CCL3, CCL11, CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, and CXCL11. IL-1 α , IL-1 β , IL-6, IL-12, IL-18, IL-23,

and IL-27 were among the pro-inflammatory cytokines found in lower concentrations. Given that cytokines and chemokines are both associated with the mechanism underlying T2DM, and these modifications regulate the inflammatory response, it is conceivable that infection with *S. stercoralis* may result in a decline in these two, which would lessen the severity of T2DM.

Effects of Strongyloides stercoralis on patients with T2DM

a. No Direct Association

Three of the five studies have associated *Strongyloides stercoralis* infection with T2DM by its mechanism to modulate cytokines and chemokine production. In comparison, the two studies have proven that *S. stercoralis* infection has no direct association with T2DM by comparison of clinical characteristics of T2DM patients with and without *S. stercoralis*. With this claim, the mechanism of *S. stercoralis* was yet to be proven to affect and manifest among T2DM patients. However, the statistical evidence by studies of Salvador et al. [26] and Yingklang et al. [15] and its result of no significant association is an assertive basis to prove that *S. stercoralis* does not provide any adverse, worsening, or protective result precisely against T2DM. Furthermore, in the study of Yingklang et al., *S. stercoralis* might increase the risk of having renal-related complications, but this effect is not varied among people without T2DM. The effects of *S. stercoralis* in renal biochemical parameters are seen in both patients with and without the infection – supporting the claim

that there is no direct association or effect of *S. stercoralis* infection on patients with T2DM.

Small to moderate sample sizes, which appear to be the most prevalent among the included articles, are the main limitation of the studies listed [26, 15, 27, 28]. Such a restriction may reduce the findings' statistical power and restrict how broadly the findings can be applied. Additionally, this study was limited by the absence of the subject's baseline characteristics and the inability to assess additional potential factors [26]. The limitations added throughout the articles include the study design, potential confounding factors that may affect observed correlations, lack of information on infection duration, absence of oral glucose tolerance testing, short follow-up period, reliance on clinical tests, and diagnosis based on small changes in HbA1c that may impact the accuracy [15, 27, 28].

Conclusion

The high prevalence of Type 2 Diabetes Mellitus (T2DM) has long been a global health problem. With the continuous search for better disease management methods, one helminth infection, namely, *Strongyloides stercoralis*, has been associated with a lower risk of T2DM development. This study wanted to investigate the potential association between T2DM and *S. stercoralis* infection, with a specific focus on host immune response. To identify the studies that would be included in the review, gathering pertinent articles, selecting studies according to the inclusion and exclusion criteria, and analysing the findings were done. A PRISMA-compliant literature search was conducted using databases like ProQuest, PubMed, Wiley, and Elsevier, alongside other citation-searching organizations/websites such as Open Access Theses and Dissertations (OATD) and Internet Archive Scholars, as part of the study. Five articles fitted the criteria for review after screening and selection. Among these studies [26, 15]. Two studies demonstrated a lack of association or an inverse relationship between T2DM and *S. stercoralis* infection. There are no statistically significant differences between groups of patients with or without strongyloidiasis and those with T2DM, specifically in the

percentage. On the other hand, three studies [27, 2, 28] revealed a connection between *S. stercoralis* and T2DM, suggesting a *S. stercoralis* is linked to lower cytokine and chemokine levels. In connection with that, an excessive pro-inflammatory cytokine and chemokine milieu is known to characterize the development of T2DM. However, only the physiopathological mechanisms that may suggest potential contributing factors were listed in the systematic review, and the discussion of the infection's direct effect on T2DM patients was not thoroughly discussed, suggesting that the comorbidity is more likely to result from an indirect relationship.

In addition, Rajamanickam et al. [2] stated in their study that *S. stercoralis* infection is linked to decreased insulin levels, cytokines associated with Th1 and Th17, adiponectin, adipisin, and glucagon. However, although these results dictate the possibility of the helminth's protective effect on diabetes-related variables and may be linked to a lower incidence of type 2 diabetes, there is insufficient evidence to support the direct relationship of *S. stercoralis* and T2DM and what it might do to patients with type 2 diabetes mellitus, also given the fact that the chosen studies provided different results.

Only limited studies venture the identification of helminth potential, such as *S. stercoralis*, against T2DM. the findings of the studies will provide further information regarding the association between *S. stercoralis* and T2DM, which may be utilized in understanding both of these conditions. Furthermore, the search and selection are limited according to strict inclusion and exclusion criteria, which might have left out other related studies.

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