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# Evaluating Helminth to Treat Type 2 Diabetes – A Review

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**Abstract**

Type 2 diabetes (T2D) is characterized by lacking production of insulin and impaired insulin sensitivity. Despite the availability of antidiabetic drugs on the market, exploration of new therapeutic drugs for treating T2D from nature remains necessary. This review provides insights on the potential of helminths and helminth derived products to modulate immune response for treating T2D. We discussed several helminths that are under investigation in animal models for treating T2D namely *Schistosoma mansoni, Nippostrongylus brasiliens*, *Litomosoides sigmodontis*, and *Strongyloides stercoralis.* Finally, application of *Schistosoma mansoni* soluble egg antigens (SEA) in T2D treatment is also reviewed.

**Keywords:** helminth, immune system, type 2 diabetes

***Abstrak***

*[Evaluasi helminth untuk pengobatan Diabetes Tipe 2 - sebuah tinjauan pustaka]*

*Diabetes tipe 2 (T2D) dicirikan oleh produksi insulin yang tidak mencukupi, maupun akibat gangguan sensitivitas insulin. Terlepas dari banyaknya obat antidiabetes yang telah tersedia di pasaran, eksplorasi sumber obat baru dari alam tetaplah diperlukan. Review ini menguraikan potensi cacing dan produk turunannya dalam memodulasi respon imun untuk mengatasi T2D. Dalam review ini kami mendiskusikan beberapa spesies cacing yang sedang diujikan pada hewan coba untuk dikembangkan guna mengatasi T2D seperti Schistosoma mansoni, Nippostrongylus brasiliens, Litomosoides sigmodontis, dan Strongyloides stercoralis. Selain itu, literatur review juga difokuskan pada penggunaan antigen telur terlarut (soluble eggs antigens, SEA) dari Schistosoma mansoni sebagai alternatif pengobatan T2D..*

**Keywords:** *helminth, sistem imun, diabetes tipe 2.*

## INTRODUCTION

Diabetes mellitus refers to chronic metabolic disorders as shown by elevated plasma glucose level because of pancreatic functional impairment to synthesize insulin, decreased insulin sensitivity, or combination of both factors.(1) Diabetes is diagnosed when the concentration of fasting blood glucose is more than 126 mg/dl (7.0 mmol/l) or when the concentration of 2-hours after meal blood glucose is more than 200 mg/dl (11.1 mmol/l).(2) Both the World Health Organization and International Diabetes Federation estimated that diabetes currently affects more than 420 million people world wide.(3, 4) The incidence rate of diabetes perpetually rising in the past decade and could potentially reach to 592 million within 15 years.(5)

Diabetes is classified into four general categories namely type 1 diabetes (T1D), type 2 diabetes (T2D), gestasional diabetes mellitus, and specific types of diabetes caused by genetics, diseases of the exocrine pancreas, and drug or chemical-induced diabetes.(1) T1D is an autoimmune disease since the immune system recognizes and attacks host β-cells pancreas, which consequently influence the capacity of β-cells to synthesize insulin.(6) On the other hand, T2D is due to inefficient production of insulin by β-cells or decreased insulin sensitivity.(3) The prevalence of T2D among adult patients is higher at around 90% to 95% compared to T1D.(7)

To date, therapies on T2D focus mainly on decreasing the level of blood glucose and Hemoglobin A1c (HbA1c).(8) Clinical studies however, underlined the continuous progression of diabetes, despite the efforts to lower the level of HbA1c.(9) Furthermore, some defects such as elevated lipolysis, decreased glucose uptake, and increased hepatic glucose production were detected as other implications of the pathogenesis of T2D.(9)

Therefore, future therapy on T2D should prohibit the development of this disease by targeting the pathogenic disturbances (i.e., maintaining β-cell function and increasing insulin sensitivity). To apply this concept, multidrug therapy with varied mechanisms of action might be introduced right away at the beginning of the therapy, while at the same time, new T2D drugs are developed.[10]

Recently, helminths obtain a limelight as future treatment for T2D due to the immunomodulating effect of these parasitic worms in their hosts by inducing type 2 immune response. This immune response is characterized by the expression of the cytokines interleukin (e.g. IL-4, IL-5, IL-9, and IL-13), production of T helper 2 (Th2) cells, and elevation level of immunoglobulin (Ig) E, eosinophilia and mastocytosis.[11] A previous study shows the correlation between immune response and glucose metabolism due to helminth infection, especially in preserving insulin sensitivity.[11] Furthermore, helminth-derived product such as *Schistosoma mansoni* soluble egg antigens (SEA) and lacto-N-fucopentaose III (LNFPIII) may also be sources of potential therapeutic agents for treating T2D since they increase sensitivity to insulin and maintain glucose-metabolism homeostasis.[12]

Nature provides untapped sources of genetic diversity and biochemical richness for health and therapeutics purposes.[13] Among these genetics richness, helminths could serve as valuable source for antidiabetic treatments, however, their true potentials have not been unraveled. This review discusses progress that has been made with respect to apply helminth as treatments for T2D. In order to obtained the most relevant and updated references, we used PubMED database and searched based on key words focusing on diabetes type 2, helminth, and soluble egg antigens. From these relevant references, we elaborated the type 2 immune responses due to helminths infections and linked with the impact on T2D.

## TYPE 2 DIABETES

Type 2 diabetes (T2D) arises when pancreatic β-cells synthesize minute amounts of insulin or when target cells display reduced insulin sensitivity (insulin resistance).[14] In many cases, T2D can only be detected after emerging complications such as heart diseases, retinopathy, nephropathy, or neuropathy.[15] It is estimated that 8.5% of the adult population worldwide live with diabetes and this percentage is envisioned to elevate in the near future.[3]

The lifestyle management (e.g. a balanced diet, sufficient physical activities, no smoking, and avoid overweight and obesity) holds a valuable key to prevent the emerging of T2D.[16, 17] Furthermore, sufficient medication is an integral aspect to balance the homeostasis of the body. Nowadays, metformin is the first line therapy to treat T2D patients since this drug significantly reduce the level of HbA1C by 1.5% and fasting plasma glucose by 20%.[18] Besides, metformin does not lead to side effects such as weight gain and hypoglycemia.[19] Drugs among the class of Sulfonylureas, e.g. glibenclamide and glimepiride are the alternative for metformin since they effectively reduce the level of HbA1C levels, but could lead to hypoglycemia.[20] DeFronzo and co-workers reported pathogenesis in T2D patients is not solely caused by pancreatic β-cells, but is also induced by other tissues such as liver, muscle, fat cells, gastrointestinal tract, kidney, brain, and pancreatic α -cells.[9] Due to this complex pathogenesis, new antidiabetic drugs remain necessary to fill the gaps in the current T2D treatment.

## TYPE 2 IMMUNE RESPONSE AGAINST HELMINTH INFECTIONS

Helminth infections dominantly provoke Th2 immune responses via activation of eosinophils, macrophage (M2), adaptive Th2 immune cells and innate lymphoid cells.[21, 22] Subsequently, innate immune cells along with $CD4^+$ T cells activate Th2 response by generating IL-4, IL-5, and IL-13 that bind to receptors with an IL-4Rα constituent.[23, 24] Although basophils do not provide a direct defensive function during helminth infection, the depletion of basophils trigger a decrease of parasite-specific IgE, eosinophils, IL-4 production, and $CD4^+$ proliferation, which overall amplify the Th2 response.[25]

During helminth infection, the Th2 cytokines IL-4 and IL-13 modulate signal transducer and activator of transcription 6 (STAT6).[26, 27] This activation inhibits transcription of peroxisome proliferator-activated receptor α (PPARα) which increase insulin sensitivity.[28] Furthermore, eosinophils and macrophages are evident to protect the sensitivity of adipocytes to insulin and to maintain metabolic homeostasis of the body.[26]

A study on the infection of *Nippostrongylus brasiliensis* in obese mouse reported weight-loss assigned to IL-13 and STAT-6-dependent and independent mechanisms.[29] Furthermore, M2 polarization and eosinophils that were triggered by helminth infection or helminth-derived product lead to the decrease of adipocyte size and the increase of the white adipose tissue (WAT)-specific insulin sensitivity and elevate uptake of peripheral glucose.[12]

## HELMINTHS AND ITS DERIVED PRODUCTS IN TYPE 2 DIABETES TREATMENT

Investigation on the correlation of helminth infections or its derived products with T2D has been done over the past decenniums. Revealing the natural potential of helminth in T2D medication, researchers focused on several species namely *Schistosoma mansoni*, *Nippostrongylus brasiliens*, *Litomosoides sigmodontis*, and *Strongyloides stercoralis*. Some reasearchers also focused on analyzing helminth-derived product such as Lewis-X-containing pentasaccharide called lacto-N-fucopentaose III (LNFPIII) that is found on schistosome egg antigens.[30, 31]

### *Schistosoma mansoni*

Parasitic trematode *Schistosoma mansoni* causes intestinal schistosomiasis in humans.[32] *S. mansoni* infection and its derived products reduce inflammation and increase glucose tolerance through the activation of eosinophils, dendritic cells, macrophages, and group 2 innate lymphoid cells.[33] Moreover, *S. mansoni* infection and products also enhance the number of Tregs and Th2 cells, as well as reduce Th1 and Th17 cells, and therefore is effective for T2D treatment.[33]

The *S. mansoni* eggs are vital for stimulating Th2 response during the infection process. The soluble egg antigens (SEA) of *S. mansoni* activate Treg responses as well as Th2-polarized responses, which both suppress the Th1 responses development (34). The *S. mansoni* eggs injection into mice promotes rapid recruitment of basophils that leads to the expression of MHC class II and the exaggeration of CD4+ cells proliferation to develop into Th2 cells.[35] Moreover, the beneficial effects of injected SEA in enhancing Th2 responses and maintaining metabolic homeostasis were observed in WAT and liver of obese mice.[12]

LNFPIII is a Lewis-X-containing glycan on schistosome egg antigens that can further be explored for treating T2D. Naturally, high concentration of LNFPIII is found in human breast milk and pregnant women urine. LNFPIII is also found as the glycan structure of stage-specific embryonic antigen -1 (SSEA-1) that is expressed on fetal brain tissue.[31, 36] Thus, LNFPIII expression is adopted by schistosome parasite in order to decrease the immune response of the host to their eggs in gut.[31] Although some studies reported that LNFPIII is a schistosome glycan [30, 37], Tundup and co-workers argued that schistosome literally express Lewis-X trisaccharide, an integrated component in the LNFPIII pentasaccharide. LNFPIII itself is made synthetically as a schistosome egg glycan to induce Th2 response.[38]

LNFPIII induces Th2 responses by triggering dendritic cell (DC) maturation via toll-like receptor 4 (TLR-4).[39] LNFPIII has the ability to increase glucose tolerance and insulin sensitivity in consequence of IL-10 production that is activated by LNFPIII-induced M2 macrophages and DC. The IL-10 reduces the inflammation of WAT and enhances the sensitivity of adipocytes towards insulin.[30] Endocytosis of LNFPIII is required in the alternative activation of M2 macrophages and DC, the antigen presenting cells (APCs) (40).

### *Nippostrongylus brasiliensis*

The hookworm *Nippostrongylus brasiliensis* infection strongly promotes Th2 immune response as well as initiates the differentiation of M2 macrophages.[41] A study conducted by Wu and co-workers (2011) proved that the infection of *N. brasiliensis* decreases fasting glucose levels in mice with high-fat-diet.[42] Moreover, infection of *N. brasiliensis* increased glucose tolerance and insulin sensitivity through a mechanism that is associated with white adipose tissue eosinophils.[42] In line with Wu and co-workers (2011), Yang and co-workers (2013) found that infection of *N. brasiliensis* could maintain glucose homeostasis and increase insulin sensitivity by way of Th2 responses induction and M2 macrophages activation in adipose tissue. In addition, STAT6 activation by IL-4 or IL-13 causes the body weight loss and the lipogenesis reduction.[29]

### *Litomosoides sigmodontis*

*Litosomoides sigmodontis* is a notorious nematode model for filariasis infection in laboratory murine species.[43] During *L. sigmodontis* chronic infection, the type 2 immune response is reinforced by basophils an thus resulting in the production of eosinophils, high amount of IgE, and type 2 cytokines production.[25] *L. sigmodontis* infection also induces the production of T helper cell-derived cytokines such as IFN-γ, IL-4, and IL-5 by $CD4^+$ T cells.[25] In addition, a study by Taylor and co workers (2009) shows that the formation of CD4(+) Foxp3(+) Treg cells is rapidly stimulated during *L. sigmodontis* infection.[44] These initial $CD4^+$ T cells expressed PPAR-*γ*, which is required for the insulin sensitivity restoration after treatment by an antidiabetic drug, pioglitazone.[45] *L. sigmodontis* infection as well as *L. Sigmodontis* antigen administration also enhance glucose tolerance and decrease epididymal adipose tissue inflammation induced by diet in obese mice.[46]

### *Strongyloides stercoralis*

*Strongyloides stercoralis* is a nematode that causes strongyloidiasis intestinal infection in humans.[47] A cross-sectional study of 259 Australian Aboriginal adults that aimed to examine the relation of *S. stercoralis* infection and T2D shows that 92

participants with previous *S. Stercoralis* infection were 61% less likely to be diagnosed with T2D than those uninfected.[48] As indicated by the authors, the induction of Th2 responses and number of eosinophils caused by chronic helminth infection might be the possible reason of this finding.[48] The infiltration of eosinophils into adipose tissues drive the recruitment and maintenance of M2, the alternatively activated macrophages that will enhance the insulin sensitivity through regulatory T cells (Treg) and IL-10.[26, 42]

A cohort study in 259 Australian Aboriginal adults shows that treatment for *S. stercoralis* ameliorate glycemic control and significantly enhance HbA1c in patients with pre-existing T2D.[49] Meanwhile, treatment for *S. stercoralis* in patients without T2D exhibits significant effects on the development of T2D and glucose intolerance.[49] A current study also shows that *S. stercoralis* infection has a preventive effect in T2D since this infection is associated with diabetes-related parameters including cytokine, hormonal, and glycemic.[50] Yet, more convincing data as well as plausible molecular mechanisms are needed in order to prove the beneficial effect of *S. stercoralis* in T2D treatment.

## HELMINTH AND ITS DERIVED PRODUCTS: A FUTURE HOPE

The explorations of helminth infections and its derived products in inducing immune response, particularly the Th2 immune response, have been done in the past few decades.[21, 22] The Th2 immune response is considered to play a potential role in metabolic process including insulin sensitivity and glucose metabolism.[26, 28, 29] Despite being relatively less studied compared to T1D, some crucial findings about the correlation of helminth infection and T2D appeared to be very promising in T2D treatments development.

The roles of helminth infection in maintaining glucose homeostasis and enhancing insulin sensitivity in T2D and obese subjects have been demonstrated in *in vivo* studies in mice.[12, 28, 29, 42] Although there is still limited evidence about the beneficial effects of helminth infection and its antigens in human, these worthwhile findings could be a stepping stone in the development of helminth as medicinal agents in T2D treatment for patients.

There is a cross-sectional study in China showing the correlation between schistosome infections with lessen prevalence of diabetes and better glucose homeostasis. In addition, there is an ongoing cluster-randomized placebo controlled study will be conducted in Indonesia to figure out the effect of helminth infection in insulin sensitivity. These two studies are predicted to fill the knowledge gaps in the potential role of helminth in T2D medication. Besides, information about helminth-related agents such as its efficacy in various group of patients (e.g. gender, age, ethnic, and gender) and its effectiveness compared to antidiabetics drugs on the market are essentially needed.[51]

Moreover, one of the helminth-derived product that might be promising for new antidiabetic agent is SEA. LNFPIII found in SEA shows positive effects in inducing Th2 responses and improving insulin sensitivity.[30, 39] Because LNFPIII is possible to be synthetically made as single compound, this antigen will be more feasible to be developed as a new therapeutic agent since the dosage forms, the therapeutic and toxic dose, as well as the metabolism of single compound will be easier to be evaluated. Beside SEA, there are other *S. mansoni* egg components that can activate Th2 response namely Omega-1 and interleukin-4-inducing principle from *S. mansoni* egg (IPSE/alpha -1).[52] Omega-1 is a T2 ribonuclease and is one of the most abundant SEA component that induces Th2 polarization through DC conditioning.[53] Omega-1 is internalized by DC via the mannose receptor (MR) and its activity depends on RNase activity and glycosylation.[54] Omega-1 has a Gal$\beta$1-4(Fuc$\alpha$1-3)GlcNAc (Lewis-X) motif as the major antenna and also other terminal glycans such as GalNAc_1-4(FucR1-3)GlcNAc (LDN-F), dyfucosylated Galβ1-4GlcNAc (LacNAc,LN) and GalNAc$\beta$1-4GlcNAc (LacdiNAc, LDN).[55] Lewis-X is an important feature of omega-1 that plays a role in Th2 polarization.[55]

Similar as omega-1, IPSE/alpha-1 is also one of the most plentiful glycoproteins that are secreted by *S. mansoni* eggs.[56] IPSE/alpha-1 has almost an identical glycosylation pattern with omega-1 as both have Lewis-X antenna and dyfucosylated LN and LDN.[57] Apart from similarity Lewis-X glycans pattern between IPSE/alpha-1 and omega-1, IPSE/alpha-1 is unable to promote a strong Th2 polarization through DC conditioning.[55] IPSE/alpha-1 activates basophils and enhances their expression of IL-4 and IL-13 cytokines, which are essential for Th2 immune responses.[58]

The ability of IPSE/alpha-1 and omega-1 in activating the host Th2 immune responses through IL-4 and DC activation escalate these antigens probability to be a part of T2D medication. Moreover, Lewis-X, helminth glycan that is found in terminal trisaccharide of LNFPIII and is expressed on core-dyfucosylated N-glycans of IPSE/alpha-1 also promote anti-inflammatory state via alternative activation of APCs.[59] Thus, both IPSE/alpha-1 and omega-1 are potential as immunotherapeutics to treat inflammatory-related diseases including T2D and obesity.

*S. mansoni* and its SEA so far receive the main limelight to be developed as a new treatment

for treating T2D. However, limited studies are available to explore the same therapeutic possibility from other helminths such as *L. sigmodontis* and *N. brasiliensis*. Although relatively shaded, these helminths have the potential to develop into new drugs due to their ability to provoke Th2 response via IL-4 activation.[25, 29] In addition, a laboratory model for the human whipworm *Trichuris trichuria* called *Trichuris muris*, should also be further considered in the quest for developing drugs for T2D [60] as this helminth induces strong Th2 responses through the IL-4/STAT6 pathway.[61] Finally, considering that helminth infection strongly induces Th2 responses and huge diversity of these phyla, there is optimism in discovering more promising species and their derived products to be developed as immunotherapeutic for T2D treatment.

## CONCLUSION

Our review summarized the potential of helminths to be applied in treating type 2 diabetes via induction of type 2 immune response. To date, *Schistosoma mansoni* (including its SEA components such as LNFPIII, IPSE/alpha-1, and omega-1), *Nippostrongylus brasiliensis*, and *Litosomoides sigmodontis* seem to be the most promising helminth candidates as therapeutic drugs given their capacity to maintain glucose homeostasis and increasing insulin sensitivity. While, other potential helminths such as *Trichuris muris* and *Strongyloides stercoralis* still need further investigation.

Despite some promising evident of helminth and helminth derived products to be applied in treating T2D patients, a number of considerations should be taken into account. Firstly, patients with T2D cannot be deliberately exposed with helminths only for improving their metabolic disorder. Secondly, the administration, dosage, and duration of helminth therapy should be examined carefully with regard to safety, side effects and toxicity to treat T2D patients.[51] At the first place, the effect of helminth infection on T2D patients should be confirmed. Subsequently, helminth's components or antigens that are responsible for the therapeutic effect should also be identified. Once these specific compounds are identified, efficacy of these molecules as new therapeutic agents can be explored. Finally, extensive *in vivo* studies are crucial to further generate unequivocal evidence in developing helminth and helminth-derived products therapeutic to treat type 2 diabetes in humans.

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