Immune modulation by helminths and the impact on the development of type 2 diabetes

Ruiter, K. de

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GENERAL INTRODUCTION

Adapted from: Helminths, Hygiene Hypothesis and Type 2 Diabetes

Karin de Ruiter*, Dicky L. Tahapary*, Erliyani Sartono, Pradana Soewondo,
Taniawati Supali, Johannes W.A. Smit and Maria Yazdanbakhsh

*Both authors contributed equally

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A SHORT INTRODUCTION TO HELMINTHS

Helminths, or parasitic worms, are multicellular organisms and represent one of the most prevalent infectious agents affecting nearly one-third of the population worldwide (1). Helminth infections are widely distributed in tropical and subtropical regions, primarily in rural areas where sanitation is poor. Soil-transmitted helminths (STHs) (main species: *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm) represent the most common species infecting humans, followed by schistosomes and filarial nematodes (1). Helminths have varied life cycles, and routes of infection can vary from direct penetration (schistosomes, hookworms), entrance via a mosquito bite (filarial worms) or through ingestion (*A. lumbricoides, T. trichiura*). Also the location of adult worms within the human body differs from the peripheral blood (schistosomes), the lymphatics (filarial worms), the intestine (STHs), or other tissues.

It was estimated that 1.45 billion people worldwide were infected with at least one species of STHs in 2010, with the majority of infections and highest burden occurring in Asia (2). When expressing the burden of helminth infections in disability-adjusted life years (DALYs), 5.2 million DALYs were attributable to STHs, 3.3 million to schistosomiasis and 2.8 million to lymphatic filariasis, meaning that helminths contribute, to the greatest extent, to the total burden of neglected tropical diseases (26 million DALYs) (2, 3). Despite this worldwide burden and presumed helminth-associated morbidities such as malnutrition, poor growth, cognitive deficits and anaemia among children with heavy and chronic STH infections (4, 5), most infections are often clinically asymptomatic and mortality due to STHs is rare (6). Interestingly, a recent analysis of the Cochrane database demonstrated that mass treatment of all children in endemic areas does not improve average nutritional status, haemoglobin, cognition, school performance or survival, although it might have nutritional benefits among helminth-infected children (7).

The high prevalence of helminth infections, and its chronic and often asymptomatic nature of infection therefore suggests a long evolutionary co-adaptation between helminths and their human host. Indeed, there seems to be an immunological interaction between helminths and their host in which helminths polarize the immune system towards a strong type 2 immune response that is believed to be associated with tissue repair (8), as well as establishment of a regulatory network, which can contribute to the control of overt immune responses to allow longer term survival of the parasite while restricting inflammation that might otherwise lead to pathology (9).

HELMINTH-ASSOCIATED TH2 RESPONSES AND IMMUNE REGULATORY NETWORK

Helminth parasites are strong inducers of type 2 immunity which involves activation and expansion of $CD4^+$ T helper 2 (Th2) cells producing the cytokines interleukin (IL)-4, IL-5, IL-9, IL-10 and IL-13, systemic and localized eosinophilia, expansion of basophils and mast cells, goblet-cell hyperplasia and the production of IgE (10). Moreover, the presence of

alternatively activated macrophages (AAMs), induced by IL-4 and/or IL-13, is a characteristic feature of the polarized Th2 response (11). The type 2 response is host protective by controlling the number of parasites through direct killing or expulsion, and inducing tissue repair, necessary to protect against the damage caused by tissue-migrating helminths (12).

Cellular immune hyporesponsiveness in individuals infected with helminths was first observed in the 1970s, when lymphocytes isolated from subjects chronically infected with *Schistosoma mansoni* showed a diminished proliferative response upon stimulation with schistosome antigens (13). Subsequently, several human studies demonstrated that chronic helminth infections, such as schistosomiasis and filariasis, result in parasite-antigen-specific immune suppression (14-17). As the responsiveness is restored after anthelmintic treatment (18-22), a causal relationship between the presence of helminths and suppression of the immune system was considered likely (23). This T-cell hyporesponsiveness is thought to be mediated by a helminth-induced regulatory network involving regulatory T cells (Tregs) and their associated regulatory cytokines IL-10 and transforming growth factor (TGF)-β (14, 24). Tregs, the subset of T cells that maintains self-tolerance in humans (23), can dampen both Th1 and Th2 cell activation (9) and can be activated during many infections, such as parasitic, viral, fungal and bacterial infections (25). Several studies in animal models and humans show that helminth infections are associated with increased Treg frequencies and/or functional capacity (26-28). Moreover, the finding that mice were cleared of parasites after the administration of antibodies to Treg surface markers (GITR and CD25) supported the concept that the induction of Tregs is part of the helminths' own survival strategy (29).

T-cell hyporesponsiveness, as observed in helminth-infected populations, is not restricted to parasite antigens but extends to bystander antigens, such as vaccines, allergens or autoantigens (9). This "spillover suppression" seems to be present particularly with increasing intensity of infection (30) and has several consequences, one of them being that infected subjects develop a regulatory network which helps to control inappropriate inflammation. Indeed, areas where helminths are endemic have been associated with a reduced prevalence of immunopathologies such as Th2-mediated allergic-diseases (reviewed in (6, 31, 32)), and Th1-mediated autoimmune diseases (33, 34).

HELMINTHS AND TYPE 2 DIABETES: AN INVERSE ASSOCIATION?

There has been an alarming increase in the worldwide burden of diabetes, especially in low- to middle-income countries (35). Rapid socioeconomic development in these countries has led to a shift in dietary habits and infrastructure that promotes overnutrition and decreased physical activity, ultimately increasing the risk for type 2 diabetes (T2D) (36). Obesity-induced chronic low-grade inflammation has been shown to be a key feature in the development of insulin resistance (IR; a decrease in insulin-stimulated glucose uptake), which is a strong predictor for the development of T2D (37, 38). Initiation of inflammation in

obesity involves inflammation of visceral adipose tissue and the liver, as well as the release of free fatty acids, which then promote systemic inflammation, reflected by increased levels of pro-inflammatory cytokines (37). As helminths can skew the immune system towards an anti-inflammatory profile, it is possible that the inflammation leading to IR is decreased, which would translate into a protective role of helminths in the development of T2D. This hypothesis is supported by the notion that there is little overlap between the proportion of children per country requiring preventive chemotherapy for STH and the prevalence of diabetes (39, 40). However, it should be noted that potential confounding factors such as relative wealth, diet and physical activity are likely to play a role in this observation.

Interestingly, a number of epidemiological studies in different populations, listed in Figure 1, have reported an inverse association between helminths and metabolic diseases (Reviewed in more detail in (41)), and a recent meta-analysis showed that individuals with a previous or current helminth infection were 50% less likely to manifest metabolic dysfunction (hyperglycaemia, T2D, metabolic syndrome or insulin resistance) compared to those uninfected (OR 0.50; 95% CI 0.38-0.66) (42). Moreover, it was shown by a study in Indonesia that subjects with a current STH infection had a lower BMI and lower levels of

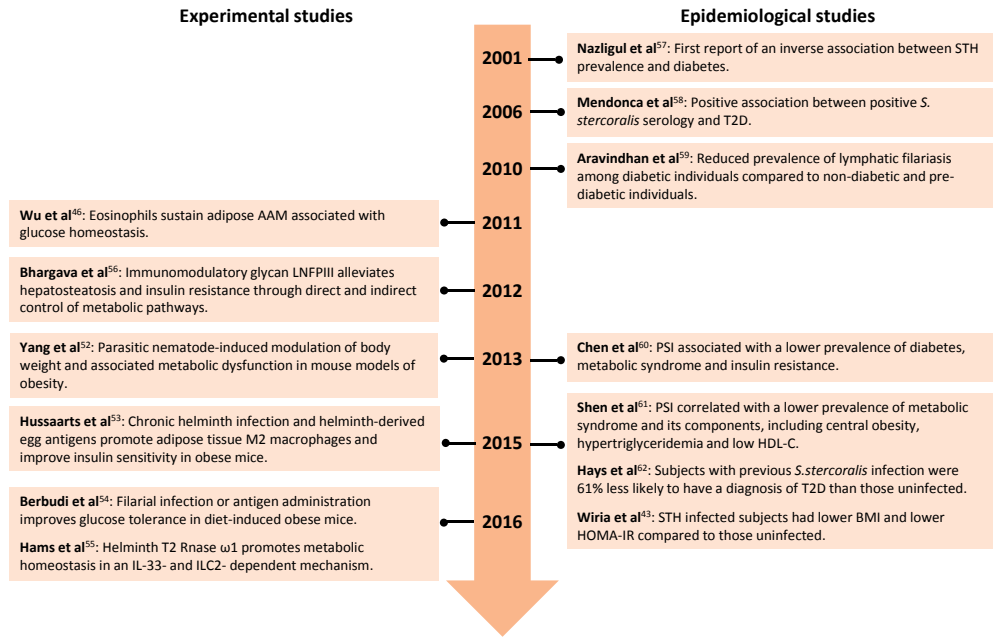

Figure 1. Overview of experimental and epidemiological landmark studies investigating the association between helminth infections or administration of helminth-derived molecules and metabolic outcomes. (AAM, alternatively activated macrophage; ILC2, innate lymphoid type 2 cells; T2D, type 2 diabetes; STH, soil-transmitted helminths; PSI, previous schistosome infection; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance).

HOMA-IR, indicating that STH-infected subjects were more insulin sensitive compared to uninfected subjects (43). A significant negative association was found between the number of helminth species a subject was infected with and HOMA-IR, even after adjustment for age, sex and BMI (43). However, cross-sectional studies provide no information on the causal relationship between helminths and metabolic diseases and therefore longitudinal studies are needed.

HELMINTHS' IMMUNOMODULATORY EFFECTS ASSOCIATED WITH IMPROVED METABOLIC HOMEOSTASIS

A number of landmark studies have provided evidence for the beneficial effects of helminths and helminth-derived molecules on metabolic homeostasis (**Figure 1**), and shed light on the immunomodulatory mechanisms that could explain the link between helminths and T2D. It was demonstrated that the maintenance of AAMs in white adipose tissue (WAT), necessary to maintain glucose homeostasis partly through secretion of IL-10 (44, 45), depends on the presence of IL-4 secreting eosinophils (46). Helminth infections promote WAT eosinophilia (46) and this accumulation is highly dependent on type 2 cytokines, particularly IL-5 (47-49). Innate lymphoid type 2 cells (ILC2s) are widely distributed in tissues, including WAT, lack antigen-specific receptors and are capable of producing type-2 cytokines in response to alarmins such as IL-25 and IL-33 (50). By functional deletion of these cells it was shown that ILC2s are required to sustain eosinophils and AAMs in WAT as they are the major source of IL-5 and IL-13 (51). These findings indicate that the presence of eosinophils, AAMs and ILC2 immune cells in WAT have beneficial effects on obesity-induced inflammation and improve glucose homeostasis in obese mice.

Recent studies have provided further evidence by demonstrating that the type 2 environment induced by infection with *Nippostrongylus brasiliensis* (52), *S. mansoni* (53) or the filarial nematode *Litomosoides sigmodontis* (54) improves glucose tolerance and insulin sensitivity in diet-induced obese mice. In addition, similar insulin-sensitizing effects have been attributed to the administration of helminth-derived (egg) antigens (53-55). Despite the different experimental models used, increased numbers of eosinophils and AAMs in WAT of helminth-infected HFD-fed mice are consistently found (52-54). By infecting eosinophil-deficient mice, it was shown that the improvement in glucose tolerance by *L. sigmodontis* infection depended on eosinophils (54). As expected, infection induced Th2 cytokine responses (IL-4, IL-5, IL-13) in WAT with IL-4 being the key cytokine consistently upregulated after infection.

In addition, *S. mansoni*-soluble egg antigen (SEA) (53), *S. mansoni* egg-derived omega-1 (ω1) (55) and *L. sigmodontis* antigen (54) administration enhanced the number of group 2 innate lymphoid cells (ILC2s) in WAT and resulted in slightly increased IL-5 (not IL-13) production (53). Recently, Hams et al. showed that ω1 induces the release of IL-33, a potent inducer of ILC2s, from adipocytes in both mice and humans (55). In the absence of ILC2s, ω1 failed to induce the infiltration of eosinophils and AAMs in WAT and was

unable to improve glucose tolerance in obese mice (55). This indicates a causative role of ILC2s in alteration of the immune cell environment in WAT.

Taken together, these findings show that in experimental animal models, helminths influence metabolic homeostasis, at least partly, by changing the immune cell composition in the adipose tissue (**Figure 2**). Whereas obesity-induced, chronic low-grade inflammation is characterized by the accumulation of $CD8^+$ T cells, $CD4^+$ Th1 cells, CAMs, B cells and mast cells in the adipose tissue, chronic helminth infections or helminth-derived molecules induce increased numbers of $CD4^+$ Th2 cells, eosinophils, AAMs, Tregs and ILC2s, dampening the inflammation and improving glucose tolerance.

SCOPE AND OUTLINE OF THIS THESIS

Although previous studies strongly suggest that there is an association between helminth infections and metabolic homeostasis, the causality of this relationship in humans has not been demonstrated as yet. Therefore, the main objective of this thesis is to improve the understanding of the role of helminth infections in the development of insulin resistance, hence T2D, and to gain insight into the immunological mechanisms underlying this possible association.

To this end, we initiated a large scale cluster randomized controlled trial (RCT), described in **Chapter 2**, assessing the effect of anthelmintic treatment on insulin resistance and other metabolic, as well as immunological parameters, in a rural area of Indonesia.

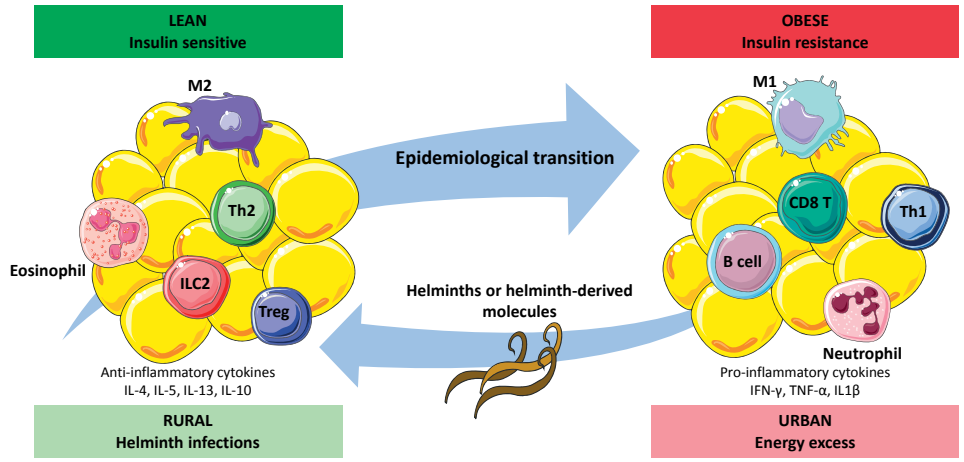

Figure 2. The effects of helminths and obesity on the immune cell composition in adipose tissue. Along with epidemiological transition, the prevalence of obesity is higher and exposure to helminth infections is lower in urban areas compared to rural areas. With obesity, the immune cell composition in the adipose tissue shifts towards a Th1 and pro-inflammatory profile associated with insulin resistance. Helminths or helminth-derived molecules are thought to prevent and/or reverse this shift by inducing a Th2 and anti-inflammatory immune cell environment, which is associated with insulin sensitivity. AAM, alternatively activated macrophages; CAM, classically activated macrophages.

This area is endemic for STH and has been previously reported to have a low prevalence of insulin resistance and T2D.

In **chapter 3**, we analyze the outcomes of this RCT with respect to the effects of anthelmintic treatment on STH prevalence, adiposity, insulin resistance and Th2 responses (e.g. eosinophil counts and total IgE levels).

Omega-1 (ω1) is a glycoprotein that was previously identified as the major immunomodulatory component in *S. mansoni*-soluble egg antigen (SEA) and in **chapter 4**, we study the effects of plant-produced recombinant ω1 treatment on whole-body glucose homeostasis and insulin sensitivity in a mouse model of diet-induced obesity. To investigate whether ω1 has a beneficial effect on metabolic homeostasis and the underlying mechanisms, we perform in-depth metabolic profiling and analyze the immune cell composition of metabolic organs.

Whereas field studies in endemic areas may be complicated by logistic challenges, there is no substitute for real-life biological settings of infection and it provides opportunities to study the underlying immunological processes that might explain the possible beneficial effects of helminth infections. **Chapter 5** describes the method that was developed to study granulocyte activation by flow cytometry in the field with only basic laboratory infrastructure. This method is applied in our RCT conducted in Indonesia in order to study the effect of anthelmintic treatment on eosinophil and neutrophil activation by assessing activation markers, the responsiveness to stimuli and circulating levels of eosinophil granule proteins, the outcomes of which are described in **chapter 6**.

Chapter 7 describes the effect of anthelmintic treatment on Th2-mediated responses in a large scale RCT in Indonesia. It measures two different components of the Th2 mediated response, namely IgE and IL-5 response to a mitogen, PHA.

To fully understand immune modulation by helminths and identify specific cells that might be important in this process, we applied mass cytometry in **chapter 8**, allowing high-resolution dissection of the cellular composition of the immune system by the simultaneous measurement of 37 cellular markers at a single-cell level. The effects of deworming on type 2 and regulatory immune responses are studied by performing unbiased immune profiling of Indonesian adults before and after anthelmintic treatment.

Finally, **chapter 9** summarizes the main findings presented in this thesis and provides directions for future research towards understanding the link between helminth infections, their immunomodulatory effects and inflammatory diseases such as T2D.

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