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Title: Helminth infections on Flores Island, Indonesia : associations with communicable and non-communicable diseases

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Summary

In this thesis we reported our investigations of the relationship between soil-transmitted helminths (STH) and a number of outcomes, in particular malaria, insulin resistance (a marker for type-2 diabetes (T2D)) and atherosclerosis (a marker for cardiovascular diseases (CVD)) on Flores island, Indonesia.

Chapter 1

Here we discussed how the major helminth infections that affect a large proportion of the population in the developing world can have impact on the immune system and the consequences of this for other infections which are co-endemic in the same areas. Furthermore, we addressed the issue of decreasing helminth infections in many parts of the world within the context of increasing inflammatory, metabolic, and cardiovascular diseases. We assembled from the available literature the evidence from experimental models and epidemiologic studies that helminth parasites appear to be able to induce immune hyporesponsiveness, which results in the host's inability to eliminate the parasites and affects the host responses to bystander antigens. In the context of malaria, while a host requires adequate pro-inflammatory responses to protect itself against malaria parasites, the inability to control overt inflammatory responses can be associated with pathology. Therefore, helminth infections might be associated with more susceptibility to malaria infection but less severe pathology. Moreover, as inflammation is a known risk factor for T2D and CVD, we addressed the possibility that helminth-induced hyporesponsiveness might have a beneficial effect on preventing the development of T2D and CVD.

Chapter 2

Here we described in detail our study protocol and our study population in the context of helminth and malaria co-infection. In order to investigate the effect of helminths on malaria infection and disease outcome, as well as on immunological parameters, the area of Nangapanda on Flores Island, Indonesia, where malaria and helminth parasites are co-endemic, was selected for a longitudinal study. A household-clustered, double-blind randomized trial, incorporating repeated treatment with albendazole (400 mg) or placebo at three monthly intervals was performed to elucidate the impact of helminth infections on malaria longitudinally. We collected information on household characteristics, anthropometry, the presence of intestinal helminths and *Plasmodium spp* infections, and the incidence of malaria episodes. Detailed methods of PCR detection of studied parasites, which were used in our trial were described, in addition to the whole blood procedures for immunological analysis of the trial.

Chapters 3 and 4

These chapters reported the outcome of the 2 years duration randomized trial. **Chapter 3** reported results of malarial parasitemia and allergy outcome, while **Chapter 4** reported the immunological outcomes. Helminth infections in our albendazole treated group decreased significantly (**Chapter 3 and 4**). However, this intensive deworming could not eliminate helminth infections. This was perhaps due to persisting helminths such as *Trichuris*, which appear not to be affected by albendazole used as a single dose at three monthly intervals as well as to the strong contribution of contaminated environment to the transmission of the helminths studied.

We found a transient increased risk of malarial parasitemia (mainly in >15 years of age) in albendazole treatment group (**Chapter 3**). However, it is still unclear what the mechanism behind the high malarial parasitemia in the treatment group is. We also showed that there did not seem to be any effect on clinical symptoms. The consistently decreasing malarial parasitemia prevalence in our study population during the study period, led to very low extent of malaria helminth co-infection than expected based on our findings during the piloting phase prior to the start of our deworming trial. This might have had an effect not only on the power of the study but also on the immunological status regarding anti malaria responses. Studies in areas with high prevalence of clinical malaria are needed to establish whether helminth infections affect this outcome.

As shown in **Chapter 4**, we found that *in vitro* immune responses were improved after albendazole treatment and significant increases in malaria-specific and mitogen-induced tumor necrosis factor and interferon γ cytokine production were observed. However, these increased pro-inflammatory responses to the malaria parasite observed during the trial may not have been sufficient to cause clinical symptoms; no changes in clinical symptoms observed in **Chapter 3**. This could also be due to the maintenance of a certain level of anti-inflammatory responses, because of incomplete deworming, which would still be able to prevent the development of clinical symptoms.

Chapter 5

There is now compelling evidence that inflammation plays a role in chronic non-communicable diseases, including CVD and T2D. In this respect, it is interesting that some chronic infections, such as helminth infections, which are highly prevalent in rural areas of low-to middle income countries, have been shown to induce anti-inflammatory and immune regulatory effects as discussed in **Chapter 1**. Here we showed in a cross-sectional manner that STH infection was associated with lower risk factors for CVD that include lower body mass index (BMI) or waist-to-hip ratio (WHR), and lower lipid levels, compared to uninfected individuals. We also noted a negative association between total IgE (TigE), which related to helminth exposure, and risk factors for CVD that included total cholesterol, low density lipoprotein and high density lipoprotein. In this study, the effect of helminth infections on CVD risk factors was at least partially mediated by an effect on BMI/WHR. However, a direct association between helminth infection and CVD markers, such as to carotid intima media thickness (cIMT) as a marker of atherosclerosis, was not seen. Indeed, the cIMT of the study participants was relatively low compared to individuals of the same age living in high income countries (HIC) and still below what is considered pathological. Further studies are necessary to assess the causal relationship between helminth infections and CVD.

Chapter 6

With respect to T2D, it has been hypothesized that chronic helminth infections by inducing anti-inflammatory responses decrease systemic inflammation and may help to prevent metabolic diseases. Here, we have shown that helminth infection was associated with improved insulin sensitivity even though there was no significant effect on fasting blood glucose (FBG) level. The improved insulin sensitivity seemed to be related, in part, to lower levels of insulin meaning that less insulin was needed to maintain normal blood glucose in individuals with helminth infections.

Chapter 7

In this chapter I discussed questions that remained or emerged from our findings. The first one is why with our intensive deworming treatment, helminth infections remained. Secondly, why we found increased risk of malarial parasitemia (mainly in >15 years of age) in the albendazole treatment group. Moreover, I questioned whether the association between helminths and CVD or T2D is similar to that seen between helminths and allergy.

First, I propose that the poor result of our intensive deworming trial could be related to highly contaminated environment and reinfection as well as to the limited efficacy of albendazole or possible emergence of drug resistance. Given that global campaigns are underway to control and eliminate STH; our finding suggests an urgent need for new approaches to helminth elimination programs. Furthermore, well-designed population studies that include adequate anthelmintic treatment regimen are needed to confirm our propositions. Diagnostic methods that are able to reveal submicroscopic infection such as *Trichuris* infection or other intestinal infections are also needed.

For the second question, I thought that the increased risk for malarial parasitemia in our study participants may have been caused by a reduced level of *Ascaris* infection. It is possible that *Ascaris* infection in the older age groups which was lower than in the younger age group prior to treatment was more effectively cleared. Therefore, the level of *Ascaris* infection might have been sufficiently high to keep malarial parasitemia at a low level in the younger age group, while the low infection after treatment in older age group was not able to do so. Whether this association between helminth and malaria is immune mediated or competition for resources is currently unknown.

In non-helminth endemic populations, allergy is associated with high levels of TlgE, while in helminth endemic populations, high levels of TlgE are associated with helminths, which are inversely correlated with allergy. Interestingly, in HIC, elevated TlgE has been shown to be associated with risk for CVD (myocardial infarction, stroke or peripheral arterial disease). In contrast, we found that TlgE levels were related to helminth exposure and we noted a negative association between TlgE and risk factors for CVD as well as association between TlgE and lower FBG. One can hypothesize that during helminth infections, the immune system may be somehow modified, that it no longer predisposes to the development of CVD. Also, chronic exposure to infections, in addition to the reduction in energy intake and association with poor nutritional status, could play an important role in the establishment of effective regulatory networks that, to a certain degree, are beneficial in preventing CVD and T2D. A possible approach will be a long-term, well-powered, placebo controlled anthelmintic trials to investigate whether alleviation of helminthic pressure is inversely correlated with anti-inflammation, lipid levels and insulin sensitivity, and therefore leads to an accelerated development of T2D and CVD.

