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Review

Do worms protect against the metabolic syndrome? A systematic review and meta-analysis

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ABSTRACT

Aims: There is increasing evidence on the role of helminth infections in modifying autoimmune and allergic diseases. These infections may have similar effect in other inflammatory processes, such as insulin resistance. This review aims to examine the literature on the effect of helminthic infections on metabolic outcomes in humans.

Methods: Using the PRISMA protocol, we searched the literature using PubMed, MEDLINE, and a manual review of reference lists. Human studies published in English after 1995 were included. Four papers were included in this review. Data was extracted and a meta-analysis was conducted using a random-effects model. Heterogeneity was assessed using Tau^2 and I^2 tests.

Results: The included studies found that infection was associated with lower glucose levels, less insulin resistance, and/or a lower prevalence of metabolic syndrome (MetS) or type 2 diabetes mellitus (T2DM). Meta-analysis showed that participants with a previous or current helminth infection were 50% less likely to have an endpoint of metabolic dysfunction in comparison to uninfected participants (OR 0.50; 95% CI 0.38–0.66).

Conclusion: This review has shown that helminth infections can be associated with improved metabolic outcomes. Understanding of the mechanisms underlying this relationship could facilitate the development of novel strategies to prevent or delay T2DM.

Contents

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1. Introduction

Helminths have co-evolved with humans over the centuries; evolutionary theory would suggest some mutual benefit for both host and parasite. Publication of the "Hygiene Hypothesis" in 1989 sparked interest in the potential protective effects of helminth infections on human disease [1] and there is now a growing body of literature exploring the role of helminths in prevention and management of certain autoimmune and allergic conditions, including coeliac disease, inflammatory bowel disease, asthma, and type 1 diabetes (T1DM) [2–4]. The apparent anti-inflammatory effect is likely to have facilitated the prolonged survival of the worm in individual hosts and over our evolutionary history. Widespread interruption of this ancient process may even elevate rates of inflammatory, autoimmune, and allergic disease.

For the last half-century, health services around the globe have endeavored to eradicate human helminth infections. In Australia, Aboriginal communities have been the focus of attention, with some researchers advocating for mass drug administration to address widespread *Strongyloides stercoralis* infection [5–8]. However, interpretation of Australian evidence on the prevalence and clinical implications of *S. stercoralis* infection has attracted some controversy [6–8]. This is because it is increasingly apparent that, for the vast majority, *S. stercoralis* causes both a chronic and asymptomatic infection [9]. The most serious and fatal manifestation of the infection, however, is disseminated strongyloidiasis. This has been seen in a small number of cases globally, typically in immunosuppressed patients [6]. Over a 10 year period in the Northern Territory, one of the most endemic areas in Australia for the worm, there were just six known cases of disseminated disease, with one fatality [6].

Coinciding with increased efforts in helminth eradication, T2DM and MetS have reached epidemic proportions across the globe [10]. Metabolic diseases place huge burdens on the health systems of both economically developed and developing societies [3]. The pathogeneses of MetS and T2DM are complex and multifactorial, but it is clear that along with nutritional factors, inflammation plays a critical role. Results from multiple studies have suggested the ability of pro-inflammatory cytokines, classically activated macrophages, and decreased T-regulatory function to drive insulin resistance in hepatic and adipose tissue [11,12]. There is also evidence that demonstrates the ability of anti-inflammatory cytokines, alternatively activated macrophages and T-regulatory cells to protect against insulin resistance in these tissues [11,12].

Recently published data from animal models have shown that helminth infections can reduce insulin resistance through modulation of immune pathways. Such observations have prompted the hypothesis that specific helminth infections may prevent or attenuate the development of insulin resistance in humans. A number of literature reviews have endeavoured to piece together the growing body of epidemiological, experimental, and clinical evidence to support this hypothesis. To date, however, there has been no systematic review or meta-analysis of this work. This paper aims to appraise and synthesise evidence from human studies examining the effect of helminth infection on host metabolic outcomes, including T2DM.

2. Methods

2.1. *Protocol and registration*

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [13]. A review protocol was registered with PROSPERO 2015, registration number CRD42015025486. It is available online.