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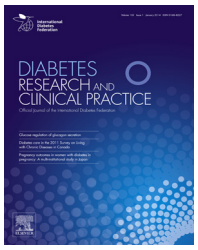

Does Strongyloides stercoralis infection protect against type 2 diabetes in humans? Evidence from Australian Aboriginal adults

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ABSTRACT

Objective: To explore the relationship between infection with *Strongyloides stercoralis* and the likelihood of having type 2 diabetes mellitus (T2DM).

Methods: Cross-sectional survey of 259 Aboriginal adults living in a remote community in northern Australia during 2013. Prior infection with *S. stercoralis* was determined by ELISA testing on serum. Main outcomes were eosinophil count, T2DM diagnosis, HbA1c, BMI, fasting lipids, Hb, blood pressure.

Findings: Ninety two participants (36%) had prior infection with *S. stercoralis* and 131 (51%) had T2DM. Those with previous *S. stercoralis* infection (ELISA titre $\geq$0.3) were 61% less likely to have a diagnosis of T2DM than those uninfected, adjusted for age, triglycerides, blood pressure and BMI using propensity score (adjusted OR = 0.39, 0.23–0.67, $P = 0.001$).

Interpretation: In this remote community where prevalence of both *S. stercoralis* and T2DM is very high, infection with *S. stercoralis* appears to be associated with a significantly reduced risk of T2DM in adults. A plausible immunological mechanism has been identified in animal models. If confirmed, this result may have practical implications for the prevention of T2DM and associated metabolic disorders in humans. This finding should be explored further with larger longitudinal studies in transitional populations where the risk of both conditions is high.

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1. Introduction and background

Strongyloides stercoralis (*S. stercoralis*) is a soil transmitted helminth (STH) infection that affects an estimated 30 to 100 million people worldwide, mostly in the developing world. The worm is transmitted through skin contact with faecal matter or contaminated soil containing the infective larva. Once established *S. stercoralis*, uniquely amongst STH infections, has the capacity for an auto-infective cycle, enabling the development of chronic infection even in the absence of further exposure. The fact that it may be asymptomatic for many years, or even decades, means that even amongst the neglected STH infections it has remained neglected. Historically, difficulty in establishing a gold standard for the diagnosis of infection, and the relative absence of effective treatment has hindered both research into and treatment of this condition [1,2].

Many of the developing countries where *S. stercoralis* is prevalent are now facing an approaching epidemic of obesity and type 2 diabetes mellitus (T2DM), however it is currently unclear whether these conditions are interrelated. Previous research has explored the potential relationship between helminth infection and chronic inflammatory diseases such as asthma, inflammatory bowel disease, and in particular, type 1 diabetes mellitus (T1DM) [3,4]. While a negative association between helminth infection and T1DM has been described, research into the relationship between T2DM and helminth infection has been limited by the fact that these two conditions, in general, only co-exist in high prevalence in ''transitional'' societies, where access to the necessary tools for the diagnosis of infection is often limited. There is however, a growing body of evidence from studies using experimental animal models to suggest that helminth infection is able to affect the development of metabolic illnesses such as insulin resistance and T2DM through a process of immunomodulation [5,6].

Very little research attention has been given to the possible interaction between *S. stercoralis* and T2DM in clinical studies. A small observational study conducted in Brazil suggested a positive association between the two conditions [7]. A larger study of risk factors for the presence of *S. stercoralis* in India, however, suggested the opposite [8]. A further study in India examined the relationship between T2DM and another chronic nematode infection, lymphatic filariasis (LF), and found a negative association. In addition they found evidence for an altered immune response in diabetic patients with LF [9].

The Aboriginal communities of Northern Australia are unique in that they are home to some of the highest recorded prevalence of *S. stercoralis* infection in the world [10] in addition to being hyper-endemic for T2DM [11]. The communities of the east Kimberley region are no exception to this. A survey of one community in 1990 registered a prevalence of 37% for *S. stercoralis* infection [12]. A recent audit of the clinic records suggested that between 20 and 30% of adults across the region have T2DM, and that approximately 50% of all adult patients presenting to the community clinics have a diagnosis of T2DM. This study setting therefore provides a possibly unique opportunity in which to examine the relationship between these two chronic illnesses. We explore here the relationship between *S. stercoralis* infection and T2DM in a transitional population where the incidence of both conditions is high.

2. Methods

2.1. Study setting

The study communities comprise three related settlements within a 100 km radius on the edge of the Tanami desert, about 800 km east of the town of Broome. The population is nearly exclusively indigenous and numbers approximately 1500 individuals spread between the three communities. Medical services are provided through the Kimberley Aboriginal Medical Services Council, which is centred in Broome. This is also the location of the nearest hospital and laboratory services.

2.2. Patients

Prior to this study very little testing or treatment of *S. stercoralis* had taken place in the study communities. There was a well-established practice of giving patients short courses (one to three days) of albendazole 400 mg for presumed helminth infection, and the occasional dose of ivermectin had been given on an empirical basis. In April 2012 the decision was made to begin testing and treating patients for *S. stercoralis* according the best practice guidelines of the Australian Strongyloides working group [13]. Accordingly, patients attending the clinic were offered testing and treatment for the infection on an opportunistic basis. As the presumed prevalence of *S. stercoralis* in the region was about 37% [12]. All indigenous patients resident in the study communities were considered to be at risk of infection.

Data was extracted including the age, sex, date of testing, *S. stercoralis* ELISA titre, haemoglobin, total eosinophil count, percentage eosinophilia, height, weight, calculated BMI, diabetic status and HbA1 C Triglyceride level, HDL and total cholesterol. Eosinophilia was defined as a total eosinophil count of 0.50×10^9/l or greater [14]. In addition, data was recorded regarding the past treatment, if any, with anthelmintic drugs. Patients were excluded from the study if they had received past treatment with ivermectin in the absence of serological testing.

2.3. Serological testing

S. stercoralis ELISA testing was ordered, often in conjunction with other routine laboratory investigations. Serological testing for *S. stercoralis* using ELISA has been shown to be adequate for both diagnostic and sero-survey purposes [15]. Testing was performed by Pathwest Laboratory in Perth Western Australia, using the commercial Strongyloides IgG ELISA (DRG laboratory). The reference values, in units of absorbance, given for this test were as follows: Less than 0.2—Negative; 0.2 to 0.4—Equivocal; Greater than 0.4—Positive. However, as was noted by the laboratory, these ranges were developed in a metropolitan population where the prevalence