Clinical Infectious Diseases

MAJOR ARTICLE

Metabolic Consequences of Concomitant *Strongyloides stercoralis* Infection in Patients With Type 2 Diabetes Mellitus

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Background. Human and animal studies have demonstrated that helminth infections are associated with a decreased prevalence of type 2 diabetes mellitus (T2DM). However, very little is known about their biochemical and immunological interactions.

Methods. To assess the relationship between a soil-transmitted helminth, *Strongyloides stercoralis* (*Ss*), and T2DM, we examined analytes associated with glycemic control, metabolic processes, and T-cell–driven inflammation at the time of *Ss* diagnosis and 6 months after definitive anthelmintic treatment. We measured plasma levels of hemoglobin A1c, glucose, insulin, glucagon, adipocytokines, and T-helper (T_H) 1-, 2-, and 17- associated cytokines in patients with T2DM with (INF group) or without (UN group) *Ss* infection. In INF individuals, we again assessed the levels of these analytes 6 months following anthelmintic treatment.

Results. Compared to UN individuals, INF individuals exhibited significantly diminished levels of insulin and glucagon that increased significantly following therapy. Similarly, INF individuals exhibited significantly diminished levels of adiponectin and adipsin that reversed following therapy. INF individuals also exhibited significantly decreased levels of the T_H1- and T_H17- associated cytokines in comparison to UN individuals; again, anthelmintic therapy augmented these levels. As expected, INF individuals had elevated levels of T_H2-associated and regulatory cytokines that normalized following definitive therapy. Multivariate analysis revealed that these changes were independent of age, sex, body mass index, and liver and renal function.

Conclusions. *Strongyloides stercoralis* infection is associated with a significant modulation of glycemic, hormonal, and cytokine parameters in T2DM and its reversal following anthelmintic therapy. Hence, *Ss* infection has a protective effect on diabetes-related parameters.

Keywords. *Strongyloides stercoralis* infection; type 2 diabetes mellitus; adipocytokines; glycemic hormones; cytokines.

The "hygiene hypothesis" initially postulated an inverse relationship between allergic diseases and bacterial infections in early childhood [1]. Consequently, the hygiene hypothesis was expanded to include helminth infections, as the immunomodulation seen in chronic helminth infection was also capable of providing a degree of protection from allergic and autoimmune diseases [2, 3]. The prevalence of helminth infections are low to absent in resource-rich (upper income) countries, which has been postulated to account for the increased incidence of allergic, autoimmune, and metabolic (eg, type 2 diabetes mellitus [T2DM]) diseases [4–6]. Epidemiological and experimental evidence suggests that helminths may play a protective role against the development of T2DM [7–13] as a result of decreases in systemic inflammation driven by the immunomodulation seen in chronic helminth infections or by alteration of the intestinal microbiota [14, 15].

T2DM, a chronic inflammatory disease characterized by persistent elevated glucose levels as a result of insulin resistance, is associated with the infiltration of macrophages and T cells into adipose tissue and increased production of proinflammatory cytokines (T-helper [T_H] 1 and T_H17) [16, 17]. T2DM can coexist with any helminth infection, although attention has focused on the major soil-transmitted helminths—namely, *Ascaris lumbricoides*, hookworm species, *Trichuris trichiura*, and *Strongyloides stercoralis* (*Ss*). Recent cross-sectional studies in India, Indonesia, and rural China, and in Aboriginal Australians, revealed that the prevalence of helminth infections in T2DM patients were significantly lower than in nondiabetic controls [9, 10, 13, 18]. These studies suggested that helminth infections may prevent or delay the onset of T2DM. Thus, in addition to the more established risk factors, such as sedentary lifestyle and high-energy foods, current deworming programs in parallel with rapid socioeconomic development could perhaps contribute to the development of T2DM in many low- and middle-income countries [19–22].

Received 5 September 2018; editorial decision 20 October 2018; accepted 5 November 2018; published online November 8, 2018.

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Clinical Infectious Diseases® 2019;69(4):697–704

DOI: 10.1093/cid/ciy935

Because little is known about the relationship between human helminth infections and metabolic diseases of inflammatory origin, we examined the interaction between *Ss* infection and T2DM and evaluated the impact of *Ss* infection on parameters important in glycemic control and those hormonal and cytokine factors previously found to be important in T2DM. To this end, we measured comprehensively the circulating levels of glycated hemoglobin (HbA1c) and blood glucose, the pancreatic hormones insulin and glucagon, the adipocytokines (adiponectin, adipsin, resistin, leptin, and visfatin), and a variety of T-cell–derived cytokines in persons with T2DM with or without coincident *Ss* infection. We also determined the effect of definitive anthelmintic treatment on the aforementioned parameters in *Ss*-infected subjects.

MATERIALS AND METHODS

Ethics Statement

All participants were examined as part of a natural history study protocol (12-I-073) approved by the institutional review boards of the US National Institute of Allergy and Infectious Diseases and the National Institute for Research in Tuberculosis (India), and informed written consent was obtained from all participants.

Study Population

We recruited 118 individuals consisting of 60 clinically asymptomatic *Ss*-infected individuals with T2DM (INF group) and 58 individuals with T2DM and no *Ss* infection (UN group) in Kanchipuram District, Tamil Nadu, South India (Table 1). These individuals were all recruited from a rural population by screening of individuals for helminth infection by stool microscopy and serology as described previously [23–26]. All the recruited individuals were between 18 and 75 years of age. None had previous anthelmintic treatment, a history of helminth infections, or human immunodeficiency virus. Individuals with other helminth infections were excluded from the study, as were pregnant or lactating women.

Table 1. Demographic Characteristics and Biochemical Parameters

Characteristic/Parameter	INF (n = 60)	UN (n = 58)
Sex		
Male	30	30
Female	30	28
Age, years, median (range)	46 (24–63)	45 (22–63)
Random blood glucose, mg/dL	179 (140–438)	180.5 (140–198)
Hemoglobin A1c, %	8.57 (6.5–12.5)	8.9 (6.5–11.8)
Urea, mg/dL	19.5 (12.34)	21.9 (11–42)
Creatinine, mg/dL	0.78 (0.3–1)	0.85 (0.6–1.0)
Alanine aminotransferase, U/L	17.7 (7–60)	22.4 (7–92)
Aspartate aminotransferase, U/L	27.8 (16–110)	24.7 (11–68)

Data are presented as geometric mean (range) unless otherwise indicated.

Abbreviations: INF, individuals with *Strongyloides stercoralis* infection with type 2 diabetes mellitus; UN, individuals with type 2 diabetes mellitus and no *Strongyloides stercoralis* infection.

Measurement of Hematological and Anthropometric Parameters

Hematological parameters were measured from fresh venous ethylenediaminetetraacetic acid blood samples on all individuals using an AcT 5diff hematology analyzer (Beckman Coulter, Brea, California). Anthropometric measurements (including height, weight, and waist circumference) and biochemical parameters (including plasma glucose, lipid profiles, and HbA1c) were obtained using standardized techniques as detailed elsewhere [27]. Serum samples were used for biochemical parameters, and plasma was used for the other measurements.

Parasitological Examination and Anthelmintic Treatment

Strongyloides stercoralis infection was diagnosed by the presence of immunoglobulin G antibodies to the recombinant protein Ss-NIE, a 31-kDa antigen derived from *S. stercoralis* L3 parasites as described previously [24, 26]. This was further confirmed by specialized stool examination with nutrient agar plate cultures [28]. Stool microscopy was used to exclude the presence of other intestinal helminth infections. Filarial infection was excluded in all study participants by virtue of being negative in tests for circulating filarial antigen. All INF individuals were treated with a single dose of ivermectin (12 mg) and albendazole (400 mg), and follow-up blood draws were obtained 6 months later. Following anthelmintic treatment, parasitological examinations were repeated after 6 months to confirm successful chemotherapy.

Determination of T2DM Status

Diabetes was defined as an HbA1c reading of ≥6.5% and/or a random blood glucose (RBG) of >200 mg/dL, according to the American Diabetes Association criteria. All the biochemical parameters were measured after overnight fasting except RBG. All diabetic individuals were referred to the primary healthcare center for diabetic treatment.

Measurement of Plasma Adipocytokines and Cytokine Levels

Plasma levels of pancreatic hormones (insulin and glucagon), adipocytokines (adiponectin, adipsin, resistin, leptin, visfatin), and the T_H1 cytokines interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin (IL) 2; the T_H17 cytokines IL-17A and IL-22; the T_H2 cytokines IL-4, IL-5, and IL-13; and the regulatory cytokine IL-10 were measured using a Bioplex multiplex assay system (Bio-Rad, Hercules, California). Transforming growth factor beta (TGF-β) and IL-17F were measured by conventional enzyme-linked immunosorbent assay according to the manufacturer's protocol (R&D Systems, Minneapolis, Minnesota).

Statistical Analysis

Geometric means (GMs) were used for measurements of central tendency. Mann-Whitney *U* tests were used to compare the

INF group to the UN group, and the Wilcoxon signed-rank test was used to compare parameters before and after treatment. Multiple comparisons were corrected using the Holm correction. Multiple logistic regression analysis by backward stepwise methods was used to identify factors that were influenced by *Ss* infection. Analyses were performed using GraphPad Prism version 7.0 (GraphPad, San Diego, California) and Stata version 15 (StataCorp, College Station, Texas).

RESULTS

Study Population Characteristics

The baseline demographic characteristics and biochemical parameters are shown in Table 1. There were no significant differences in age, sex, body mass index, or other biochemical parameters between the 2 groups.

Diminished Circulating Levels of Pancreatic Hormones, Adiponectin, and Adipsin in INF Individuals

To assess the effect of *Ss* infection on indices of glucose control in T2DM, we measured the levels of HbA1c and RBG in INF and UN individuals. As shown in Figure 1A, HbA1c and RBG levels were not different between the 2 groups. We next measured insulin and glucagon in INF and UN individuals. As shown in Figure 1A, the levels of insulin (GM, 35.97 vs 61.09 pg/mL; $P = .0254$) and glucagon (GM, 175.1 vs 240.3 pg/mL; $P < .0001$) were significantly lower in INF compared to UN individuals. respectively. Next, we assessed the effect of *Ss* infection on adipocytokines in T2DM. We measured the plasma levels of adiponectin, adipsin, resistin, leptin, and visfatin in INF and UN individuals. As shown in Figure 1B, INF individuals exhibited significantly lower levels of adiponectin than UN individuals (GM, 133 808 vs 209 547 pg/mL, respectively; $P = .0228$) and adipsin (GM, 14 726 vs 26 109 pg/mL, respectively; $P = .0323$). Thus, *Ss* infection is associated with lower circulating levels of the pancreatic hormones, adiponectin, and adipsin in *Ss*-infected subjects with T2DM.

Diminished Circulating Levels of T_H1 and T_H17 Cytokines and Elevated Levels of T_H2 Cytokines and TGF-β in INF Individuals

To determine whether helminth infections might improve inflammatory processes by reducing potentially pathological T_H1 and T_H17 immune responses, we measured the circulating levels of T_H1-associated (IFN-γ, TNF-α, and IL-2) and T_H17-associated (IL-17A, IL-17F, and IL-22) cytokines in INF and UN individuals. As shown in Figure 2A, INF individuals had significantly lower levels of IFN-γ compared with UN individuals (GM, 280.1 vs 344 pg/mL; $P < .0001$), TNF-α (GM, 414.4 vs 528.3 pg/mL; $P = .0081$), IL-2 (GM, 109.8 vs 148.8 pg/mL; $P = .0252$), IL-17A (GM, 318 vs 394.1 pg/mL; $P = .0087$), and IL-17F (GM, 121.8 vs 141.9 pg/mL; $P = .0186$). In contrast, INF

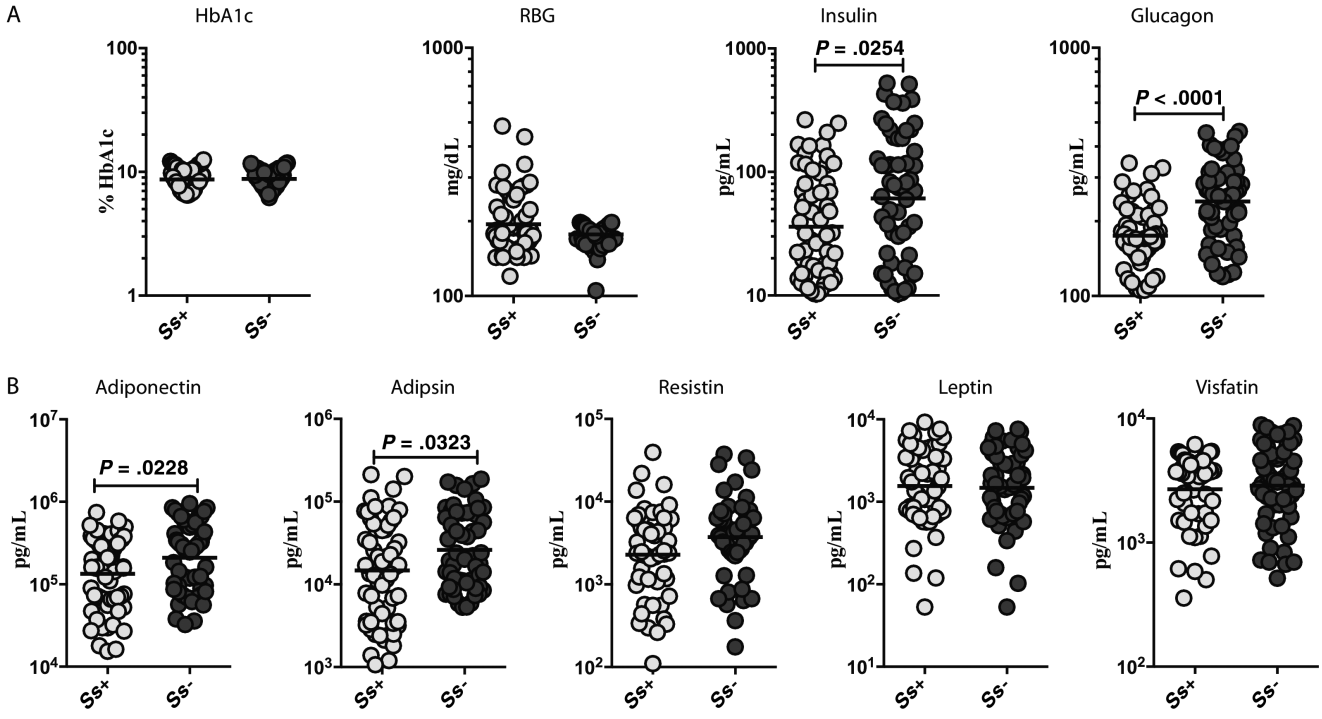

Figure 1. Diminished circulating levels of pancreatic hormones, adiponectin, and adipsin in individuals with *Strongyloides stercoralis* infection with type 2 diabetes mellitus (INF). *A*, Plasma levels of glycated hemoglobin, random blood glucose, insulin, and glucagon in the INF and UN (individuals with type 2 diabetes mellitus and no *S. stercoralis* infection) groups. *B*, Plasma levels of adiponectin, adipsin, resistin, leptin, and visfatin in the INF and UN groups. Each dot is an individual subject with the bar representing the geometric mean. Abbreviations: HbA1c, glycated hemoglobin; RBG, random blood glucose; *Ss*, *Strongyloides stercoralis*.

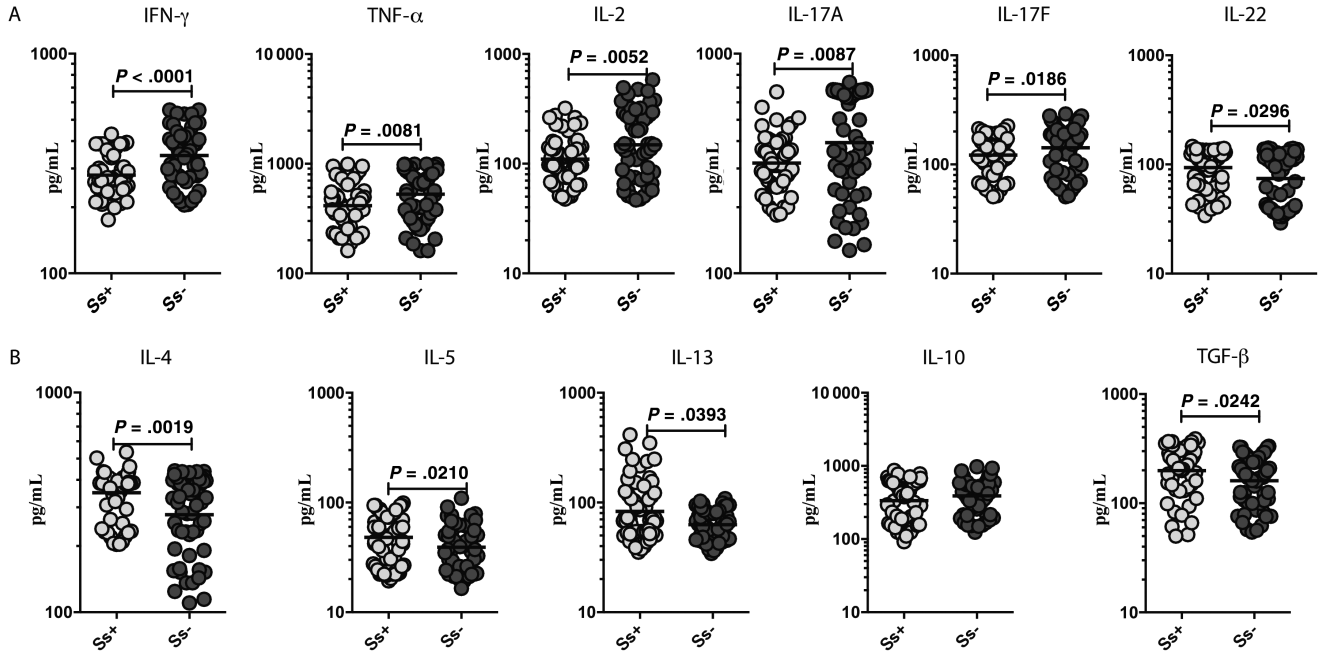

Figure 2. Diminished circulating levels of T-helper (T_H) 1 and T_H17 cytokines and elevated levels of T_H2 cytokines and transforming growth factor beta (TGF-β) in individuals with *Strongyloides stercoralis* infection with type 2 diabetes mellitus (INF group). *A*, Plasma levels of T_H1 cytokines (IFN-γ, TNF–α, and IL-2) and T_H17 cytokines (IL-17A, IL-17F, and IL-22) in the INF and UN (individuals with type 2 diabetes mellitus and no *S. stercoralis* infection) groups. *B*, Plasma levels of T_H2 (IL-4, IL-5, and IL-13) and regulatory (IL-10 and TGF-β) cytokines in the INF and UN groups were measured. Each dot is an individual subject with the bar representing the geometric mean. Abbreviations: IFN-γ, interferon gamma; IL, interleukin; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; *Ss*, *Strongyloides stercoralis*.

individuals had significantly higher levels of IL-22 (GM, 93.36 vs 74.26 pg/mL; $P = .0296$) in comparison to UN individuals.

Chronic helminth infection has been shown to protect against metabolic disorders by promoting a T_H2 (and/or a regulatory) response [29]. To determine the effect of *Ss* infection on the T_H2-associated and regulatory cytokines in T2DM, we measured the plasma levels of T_H2-associated (IL-4, IL-5, and IL-13) and regulatory (IL-10 and TGF-β) cytokines in INF and UN individuals. As shown in Figure 2B, IL-4 (GM, 349.7 vs 278 pg/mL; $P = .0019$), IL-5 (GM, 48.19 pg/mL vs 39.14 pg/mL; $P = .0210$), IL-13 (GM, 83.11 vs 62.77 pg/mL; $P = .0393$), and TGF-β (GM, 199.2 vs 160.6 pg/mL; $P = .0242$) levels were significantly elevated in INF vs UN individuals. Thus, *Ss* infection with T2DM is associated with lower circulating levels of T_H1- and T_H17-associated cytokines and higher circulating levels of IL-22, the T_H2- associated cytokines, and TGF-β.

Changes in Circulating Levels of Pancreatic Hormones, Adiponectin, and Adipsin Following Anthelmintic Treatment

Next, we wanted to determine the effect of anthelmintic treatment on the levels of HbA1c, RBG, and the pancreatic hormones insulin and glucagon. As shown in Figure 3A, the posttreatment levels of HbA1c (percentage increase of 25%; $P < .0001$), RBG (percentage increase of 18%; $P < .0001$), insulin (percentage increase of 13%; $P = .0101$), and glucagon (percentage increase of 18%; $P < .0001$) were significantly increased compared with pretreatment levels.

To determine the effect of anthelmintic treatment on adipocytokines, we measured the circulating levels of adiponectin, adipsin, resistin, leptin, and visfatin in INF individuals 6 months following anthelmintic treatment. As shown in Figure 3B, the levels of adiponectin (percentage increase of 14%; $P = .0328$) and adipsin (percentage increase of 12%; $P = .0120$) levels were significantly elevated in INF individuals posttreatment compared with their pretreatment levels.

Elevated Levels of T_H1 and T_H17 Cytokines and Diminished Levels of T_H2 Cytokines and TGF-β Following Anthelmintic Treatment

To determine the effect of anthelmintic treatment on circulating levels of T_H1-associated (IFN-γ, TNF-α, and IL-2) and T_H17-associated (IL-17A, IL-17F, and IL-22) cytokines, we measured the cytokines in INF individuals at 6 months following anthelmintic treatment. At 6 months following anthelmintic treatment, the levels of IFN-γ (percentage increase of 16%; $P = .0015$), TNF-α (percentage increase of 6%; $P < .0001$), IL-2 (percentage increase of 18%; $P = .0201$), IL-17A (percentage increase of 22%; $P = .0017$), and IL-17F (percentage increase of 21%; $P = .0324$) all increased following treatment, whereas the IL-22 (percentage decrease of 15%; $P < .0001$) levels were lower than the pretreatment levels (Figure 4A).

Next, we wanted to determine the effect of anthelmintic treatment on T_H2-associated and regulatory cytokines. We measured the T_H2 and regulatory cytokines in INF individuals at 6 months following anthelmintic treatment. As shown

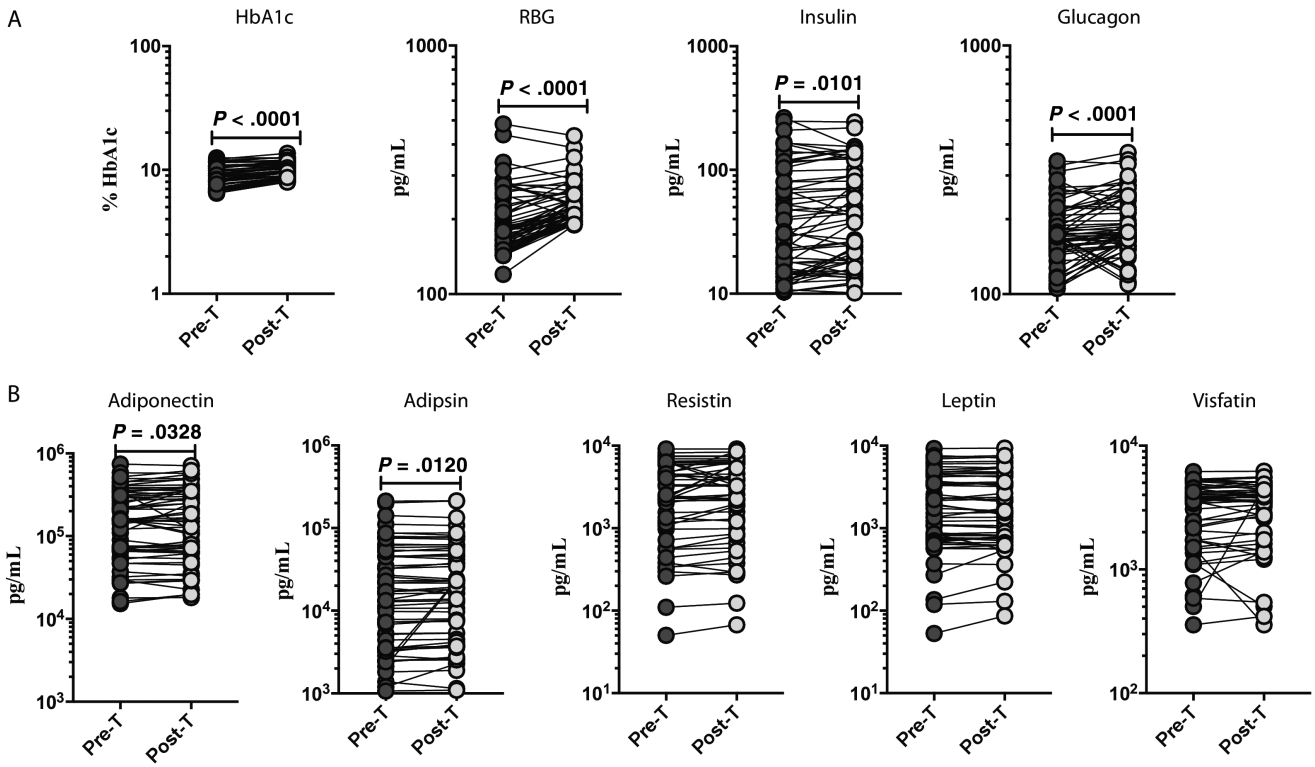

Figure 3. Heightened circulating levels of pancreatic hormones, adiponectin, and adipsin following anthelmintic treatment. *A*, Plasma levels of HbA1c, RBG, insulin, and glucagon in individuals with *Strongyloides stercoralis* infection with type 2 diabetes mellitus (INF) Pre-T and 6 months post-T were measured. *B*, Plasma levels of adiponectin, adipsin, resistin, leptin, and visfatin in INF individuals Pre-T and 6 months Post-T were measured. Abbreviations: HbA1c, glycated hemoglobin; Pre-T, pretreatment; Post-T, posttreatment; RBG, random blood glucose.

in Figure 4B, IL-4 (percentage decrease of 9%; $P = .0001$), IL-5 (percentage decrease of 9%; $P < .0001$), IL-13 (percentage decrease of 9%; $P = .0302$), and TGF-β (percentage decrease of 22%; $P = .0009$) levels were lower in comparison to their respective pretreatment levels.

Multivariate Regression Analysis of Helminth–T2DM Interaction

Multivariate regression analysis was done to assess the influence of *Ss* infection on the various analytes assessed in this study in T2DM individuals. As shown in Table 2, after adjusting for the effects of age; sex; body mass index; and levels of creatinine, alanine aminotransferase, and aspartate aminotransferase, the levels of RBG, adiponectin, IFN-γ, IL-2, TNF-α, IL-17F, IL-4, IL-13, and TGF-β were all significantly influenced by *Ss* infection. Thus, our data confirm that *Ss* infection has a profound influence on various important parameters in individuals with T2DM, including blood glucose levels, and levels of the adipocytokines and the more conventional cytokines.

DISCUSSION

T2DM is a state of chronic inflammation with alterations in cytokines and chemokines, activation status of different cell types, and metabolic perturbations in various organs [30]. Helminth infections are known modulators of all of the above responses due to their propensity to control detrimental inflammatory responses and support metabolic homeostasis both locally and systemically [31]. Recent studies have shown that helminths may confer protection against the development of T2DM [7, 8], probably by altering host immune responses. Thus, it has been postulated that elimination of helminth infections could contribute to the development of T2DM in many of the economically advanced countries [19]. Previous studies have shown that alterations in the gut microbiota modulate glucose intolerance and adipose tissue inflammation and that helminth infections could alter the gut microbiome during obesity and modulate glucose uptake, inflammation, and insulin sensitivity [32]. Thus, the helminth infection–T2DM interface appears to be counterregulatory, with the effects of helminths on diabetic status still to be fully explored.

We thus first explored the influence of *Ss* infection on parameters associated with glycemic control in T2DM individuals. Although *Ss* infection had no significant effect on of HbA1c and RBG in those with coincident T2DM, treatment of *Ss* infection clearly caused a worsening of both the HbA1c and RBG levels, a finding suggestive of helminth infection–induced modulation of hyperglycemia and perhaps insulin resistance. We speculate that the absence of an effect at baseline could depend on the duration of *Ss* infection and/or infection load, which is variable

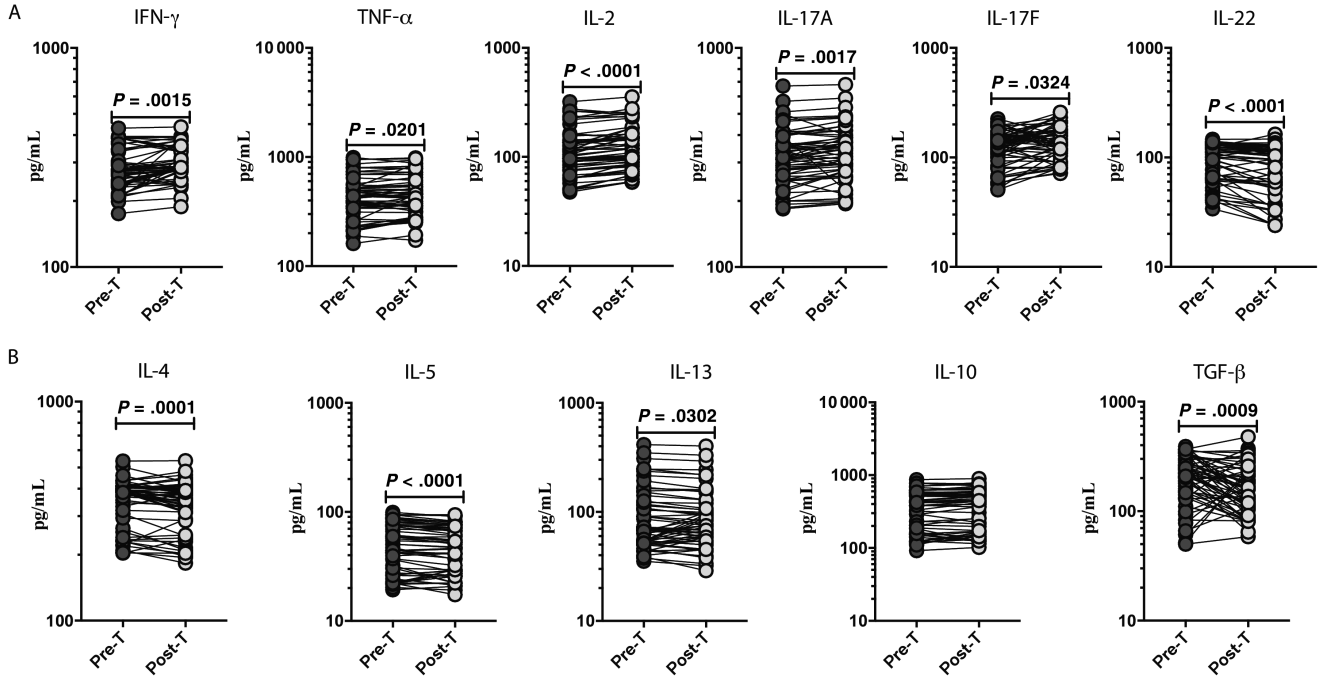

Figure 4. Heightened circulating levels of pancreatic hormones, adiponectin, and adipsin following anthelmintic treatment. *A*, Plasma levels of T-helper (T_H) 1 cytokines (IFN-γ, TNF–α, and IL-2) and T_H17 cytokines (IL-17A, IL-17F, and IL-22) in individuals with *Strongyloides stercoralis* infection with type 2 diabetes mellitus (INF group) Pre-T and 6 months Post-T were measured. *B*, Plasma levels of T_H2 cytokines (IL-4, IL-5, and IL-13) and regulatory cytokines (IL-10 and TGF–β) in the INF group Pre-T and 6 months Post-T were measured. Abbreviations: IFN-γ, interferon gamma; IL, interleukin; Pre-T, pretreatment; Post-T, posttreatment; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

in different individuals. In T2DM, insulin deficiency occurs as pancreatic β-islet cells fail to compensate for insulin resistance by increasing the production of insulin or for a reduction of β-islet cell mass as a consequence of β-islet cell apoptosis [33]. Indeed, previous studies have shown that helminths might protect against insulin resistance in T2DM [9]. In line with this, the present study has demonstrated that *Ss* infection was associated with lower insulin and glucagon levels, levels that reversed following anthelmintic treatment. However, our study did not reveal any direct correlation between infection load and biochemical parameters.

An imbalance between pro- and anti-inflammatory adipokines could also contribute to the development of insulin resistance. Adiponectin is an anti-inflammatory adipokine that is most the abundant adipokine in plasma. Adiponectin, as a modulator of inflammation in a variety of diseases, has recently been highlighted [34]. Circulating adiponectin levels are generally positively correlated with insulin sensitivity [35]. Adipsin was recognized as a proinflammatory product of adipose tissue that is induced in models of diabetes and obesity, providing evidence for a functional link between obesity and inflammation. A recent study shows that measurement of adipsin levels may be used,

Table 2. Multiple Logistic Regression Analysis on Effect of *Strongyloides stercoralis* Infection on Type 2 Diabetes Mellitus

Factors	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Hemoglobin A1c, %	0.979 (.788–1.216)	.851	0.695 (.401–1.206)	.197
Random blood glucose, mg/dL	1.013 (1.002–1.023)	.015	1.013 (1.001–1.024)	.029
Adiponectin, pg/mL	0.999 (.999–.999)	.012	0.999 (.999–.999)	.005
IFN-γ, pg/mL	0.989 (.984–.994)	.000	0.964 (.940–.988)	.004
IL-2, pg/mL	0.993 (.989–.997)	.001	0.979 (.965–.993)	.004
TNF-α, pg/mL	0.997 (.996–.999)	.003	0.994 (.989–.999)	.025
IL-17F, pg/mL	0.991 (.985–.998)	.011	0.976 (.958–.995)	.016
IL-4, pg/mL	1.006 (1.002–1.011)	.001	1.013 (1.006–1.020)	≤.001
IL-13, pg/mL	1.016 (1.005–1.028)	.005	1.029 (1.010–1.049)	.003
TGF-β, pg/mL	1.005 (1.000–1.009)	.019	1.005 (1.000–1.010)	.043

Abbreviations: CI, confidence interval; IFN, interferon; IL, interleukin; OR, odds ratio; TGF, transforming growth factor; TNF, tumor necrosis factor.

from a diagnostic standpoint, to identify those patients at high risk of developing β-islet cell failure and accelerated diabetes [36]. In animal models, mice lacking adipsin have worsened glucose homeostasis when placed under the metabolic stress of diet-induced obesity [37]. We have shown that both adiponectin and adipsin are present at diminished levels in the circulation in INF individuals. These levels were significantly increased following anthelmintic treatment, a finding that suggests that *Ss* infection may modulate adipocytokine levels in INF individuals. Previous studies did not report any difference in adipocytokine levels between individuals with coronary artery disease and coincident helminth infection and those with coronary artery disease alone [38]. In the current study, resistin, leptin, and visfatin were similar between the 2 groups. Thus, modulation of adipocytokines is another mechanism by which helminths could influence glucose homeostasis and insulin resistance in T2DM.

Helminth infections are associated with modulation of the immune responses, including those associated with innate and adaptive responses [39]. We have previously shown that the cytokine profile of *Ss*-infected asymptomatic individuals had significantly diminished circulating levels of the proinflammatory cytokines and significantly elevated levels of the T_H2-associated and regulatory cytokines [40]. The induction of both the T_H2-associated and regulatory cytokine responses is postulated to contribute to the modulation of proinflammatory, T_H1, and T_H17 cytokine responses [31]. A previous study from a high-fat diet–induced mouse model of diabetes showed increased T_H2/Treg-associated functional activity and reduction in the levels of IFN-γ and IL-17 compared with helminth-uninfected control mice [11]. In addition, previous reports indicate that $CD4^+$ T cells producing IL-17A and IFN-γ drive inflammation and may lead to insulin resistance [41, 42].

In our study, T_H1 (IFN-γ, TNF-α, and IL-2) and T_H17 (IL-17A and IL-17F) cytokines were significantly lower in INF individuals than in those without *Ss* infection. Thus, our data suggest that a mechanistic underpinning of the helminth–diabetes interface involves the modulation of T_H1 and T_H17 cytokine responses, which has the propensity for improving insulin sensitivity and for promoting barrier function and tissue repair through IL-22 induction [43] (Figure 2). T_H2-associated cytokine production is the hallmark of the host response to helminth infection [39]. Helminth infections are also associated with expansion of T cells producing the regulatory cytokines IL-10 and TGF-β [44, 45], which promote insulin sensitivity by inducing the development of alternatively activated macrophages, by promoting eosinophilic infiltration of adipose tissue and by activation of innate lymphoid cells [41, 46].

In summary, our study demonstrates that *Ss* infection may provide a degree of protection against the severity of T2DM by modulating adipocytokines and the associated cytokine milieu. Our data provide an important link between soil-transmitted helminth infection and the modulation of the severity of T2DM and also opens up novel avenues to reach better glycemic control through a better understanding of helminth-driven immune-mediated and nonimmune-mediated alteration of host metabolism.

Notes

Acknowledgments. The authors thank Dr Satiswaran and Prabbu Balakrishnan for valuable assistance in collecting the clinical data for this study, N. Pavan Kumar for technical assistance, and the staff of the Department of Epidemiology, National Institute for Research in Tuberculosis, for valuable assistance in recruiting the patients for this study.

Financial support. This work was supported by the Intramural Research Program of the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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