

James D'Silva, School of Clinical Medicine
Supervised by Dr Rafael Di Macro Barros

Can Helminths be Modelled as 'Old Friends' to the Human Immune System and Metabolism?

1. Introduction

Helminths are parasitic worms. They are found in our soils, freshwater and livestock and have lived with and threatened humans for millions of years. The 'Old Friends' hypothesis proposes that our immune system may have evolved dependence on worm exposure. The hypothesis is that to survive in their human host longer, helminths suppress the immune system, which protects the host from allergic, autoimmune and inflammatory diseases. This literature review investigates evidence of the 'Old Friends' hypothesis in experimental mouse models and clinical trials in humans.

2. Helminth Life Cycles

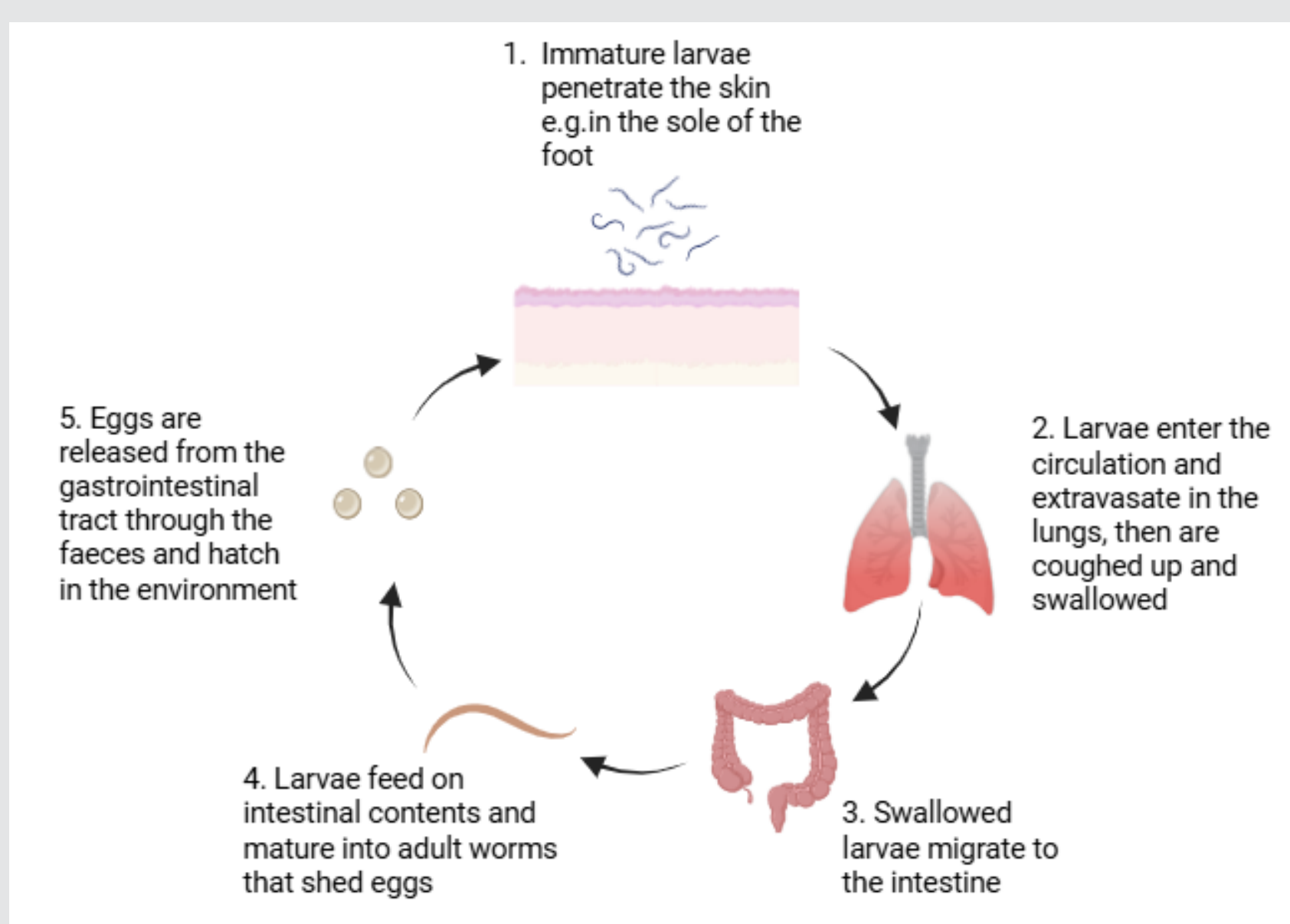


Figure 1. The prototypic lifecycle of *Ancylostoma duodenale*

Worms migrate invasively through multiple tissues in order to settle in the intestine. This destruction challenges the immune system, and the ability of helminths to establish long-term residence and successful reproduction whilst minimising pathology. One solution that worms have evolved is to suppress the immune system.

3. The Immune Response

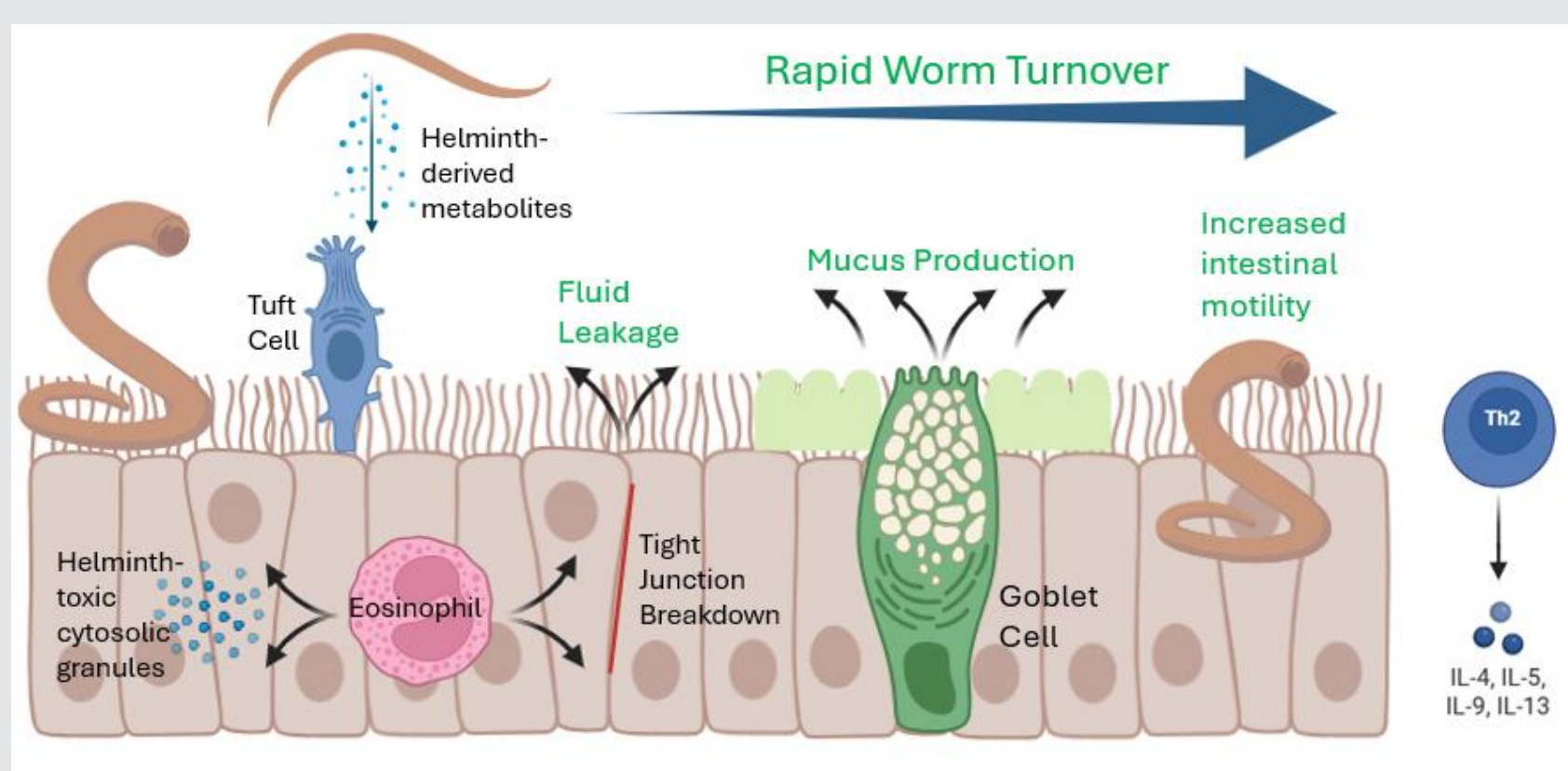


Figure 2. The 'weep and sweep' immune response to clear helminths. The adaptive immune response is specific to the type of threat (i.e. helminth, bacteria, virus).

The response to helminth infection is orchestrated by Th helper (Th) cells. Th2 drives the innate 'weep and sweep' response whereas regulatory T cells (Tregs) attenuate things to minimise collateral damage, enable tissue repair and maintain intestinal barrier homeostasis. Such immunosuppression can be beneficial in the context of autoimmune and inflammatory disease.

4. Friend - Immunology

Inflammatory Bowel Disease (IBD) is proposed to result from a failure to downregulate a chronic Th1 intestinal inflammatory process. Induction of a Th2 immune response by intestinal helminths or their eggs diminishes Th1 responses. In theory, this could treat IBD. Promising early phase trials showed that eggs from the pork whipworm *Trichuris Suis* (TSO) were a safe and possibly effective treatment for IBD, achieving remission in 9/11 participants (Summers et al, 2003). However, larger randomised-controlled studies failed to replicate this as TSO showed no clinical superiority versus placebo.

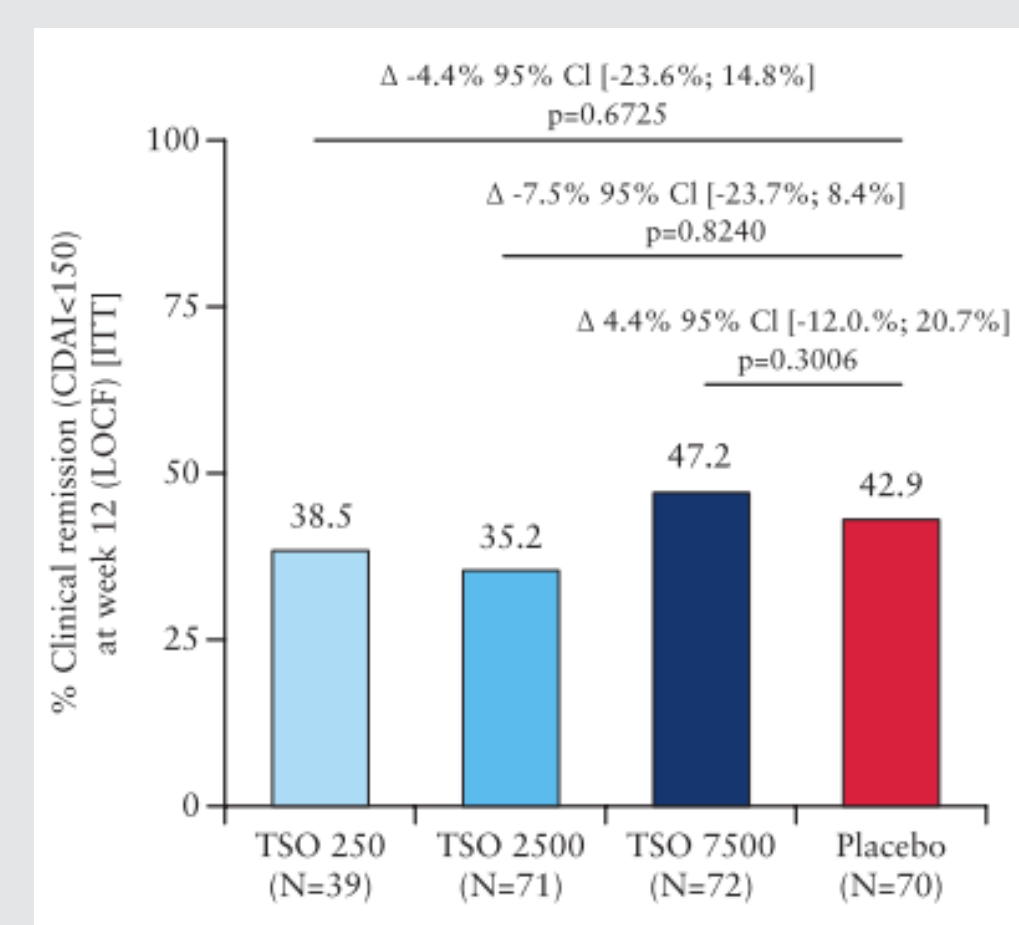


Figure 3. Clinical Remission from Crohn's Disease at 12 Weeks with TSO and Placebo. (Schölmerich et al, 2016)

5. Friend - Metabolism

The prevalence of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM) has risen dramatically in developed nations. Studies reveal a link between metabolism and immunity, which can be targeted by helminth therapy. Indeed, cells associated with Th2 immunity predominate in lean white adipose tissue, whereas those associated with Th1 immunity predominate in obesity.

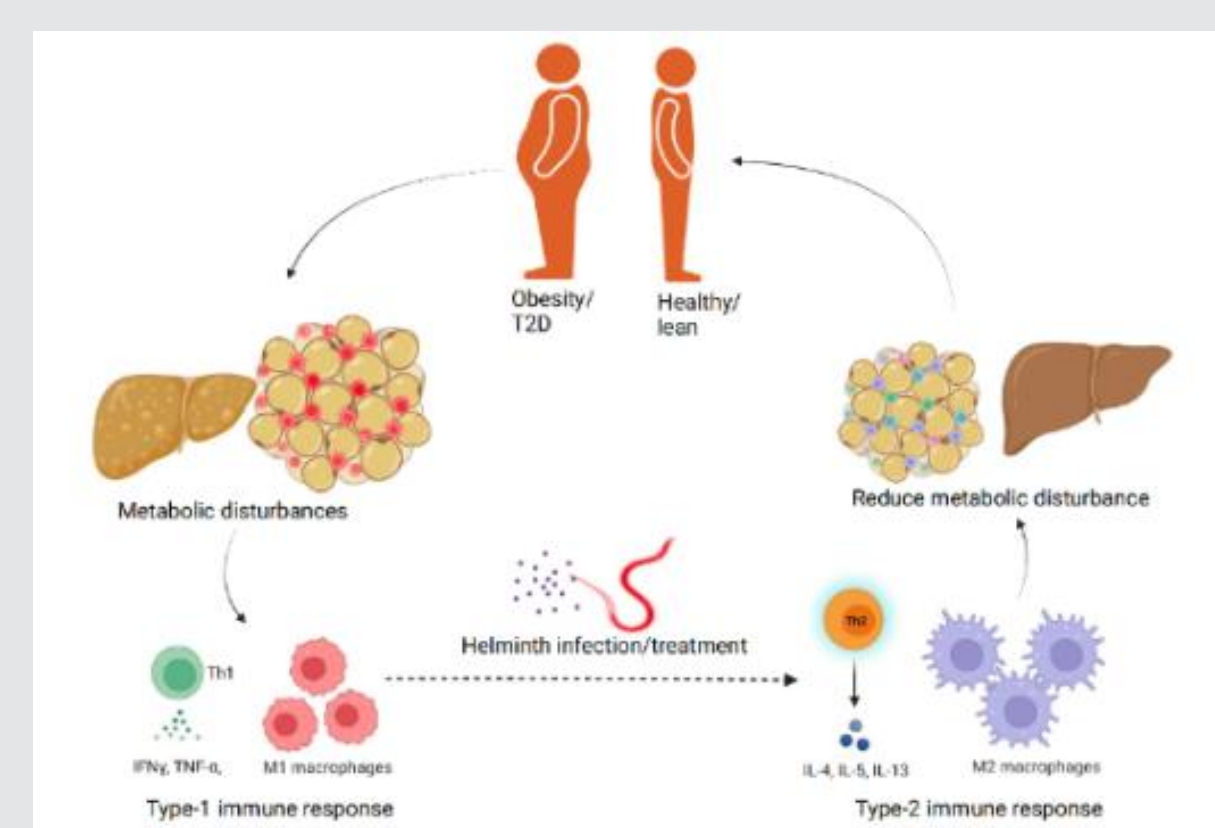


Figure 4. The immune response in a healthy and obese/insulin-resistant state (Sikder et al, 2024).

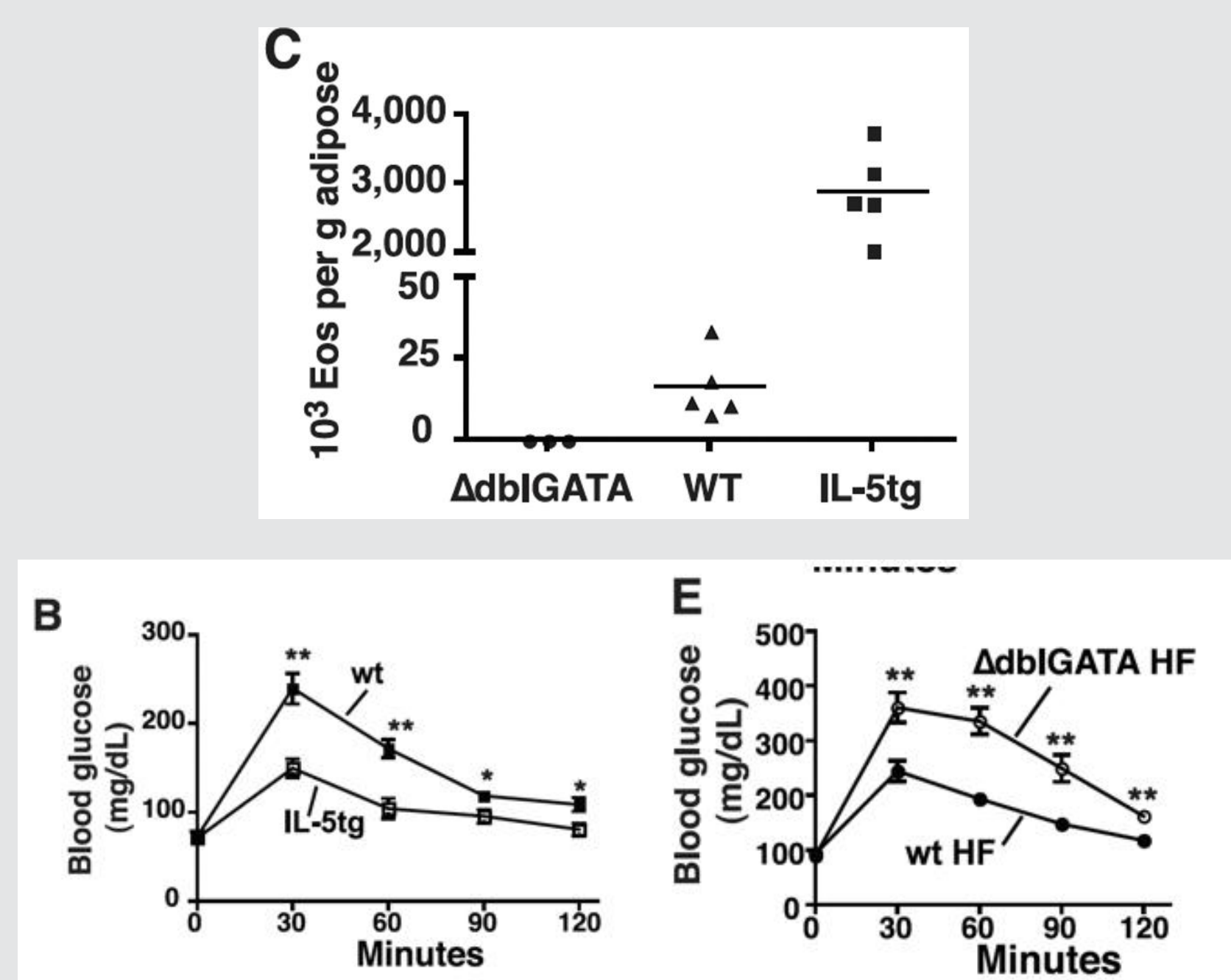


Figure 5. Mice rendered transgenic for IL-5 harbour eosinophilia, less adipose and increased insulin sensitivity to glucose challenge (Wu et al, 2011).

IL-5 is a core cytokine produced by Th2 cells and others in the Th2 response. IL-5 transgenic mice are enriched in fat-infiltrating eosinophils and accumulate less fat when fed a high-fat diet. The effect is reproduced in wild-type mice infected with helminths. Moreover, humans challenged by infection with the gastrointestinal roundworm *Nippostrongylus brasiliensis* experience measurable improvements in insulin sensitivity.

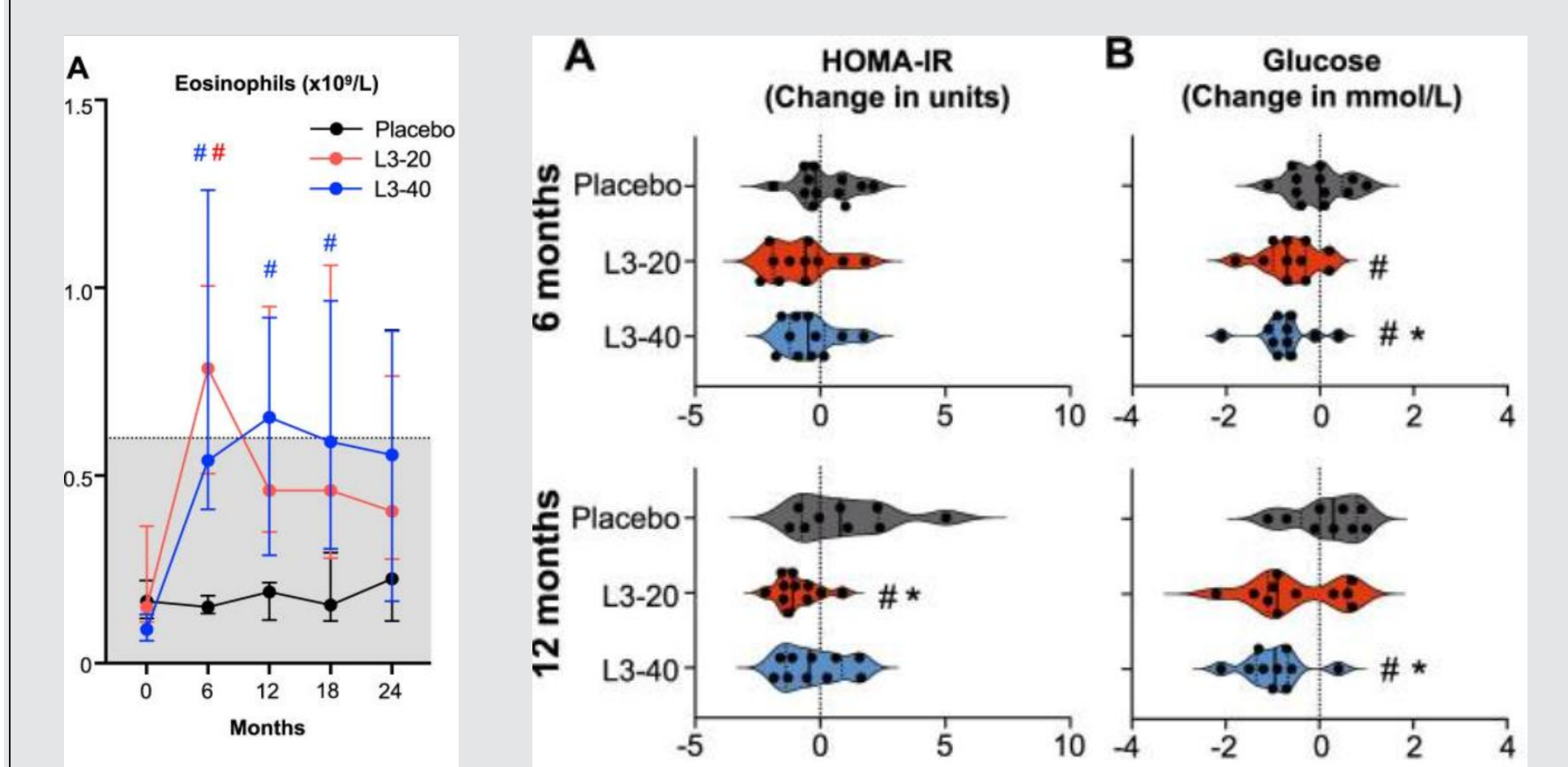


Figure 6. A human trial of patients with metabolic syndrome infected with the hookworm *Necator americanus* (L3-20 and L3-40) Homa-IR is a measure of insulin resistance and Glucose is a measure of resting blood glucose (Pierce et al, 2023).

6. Foe

In areas where sanitation, hygiene and clean water access are poor, soil-transmitted helminths are highly prevalent.

Uncontrolled worm secretions can have undesirable immunological effects. By inducing a state of systemic immune suppression, helminths can blunt responses to vaccination (Natukunda et al, 2022).

Helminths scavenge nutrients from their host, and in the process induce tissue damage, blood loss and chronic intestinal inflammation impairing nutrient absorption. Females of child-bearing age are particularly vulnerable to protein and iron-deficient malnutrition caused by helminths.

7. Conclusion

The relationship of helminths with humans can be looked at from 2 perspectives

- From a global health perspective, the eradication of helminths should be pursued.
- From a therapeutic perspective, there is sufficient data to show that the interaction of helminths and the immune system has lots of potential in the management of non-communicable metabolic and inflammatory diseases.
- With increased understanding of the cellular and molecular pathways involved in the host: helminth interaction, novel drug targets to treat metabolic and immune pathologies are likely to be revealed.

References

1. Summer et al, 2003, American Journal of Gastroenterology
2. Schölmerich et al, 2016, Journal of Crohn's and Colitis
3. Sikder et al, 2024, Elsevier
4. Wu et al, 2011, Science
5. Pierce et al, 2023, Nature
6. Natukunda et al, 2022, Parasite Immunology