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Dear Colleague,
We are pleased to inform you that the peer review process and editorial review process have been completed for your following manuscript.

Manuscript Number: 2024/IJTDH/124181

Title: Metabolic Shifts Induced by Helminth Infections and Their Contribution to Stunting in Vulnerable Populations

Author(s): Trini Suryowati

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Metabolic Shifts Induced by Helminth Infections and Their Contribution to Stunting in Vulnerable Populations

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Aims: to revisit the condition of chronic metabolic shifting caused by immunomodulatory sequence facilitated by helminth infection together with other deteriorating condition such as persistent exposure to infection which contributes to stunting formation.
Discussion: During dynamic interaction between active helminth infection and the host, the helminth and its excretory/secretory products induce and arouse the type 2 immune response which drives host tolerance and plays an important role in promoting tissue repair. Helminths also activates M2 Macrophages and induce a metabolic shift, even metabolic reprogramming towards reliance on oxidative phosphorylation, lipid oxidation and amino acid metabolism. Helminth-induced activation and metabolic reprogramming of macrophages precede the improvement in overall whole-body metabolism, denoted by improved insulin sensitivity, body mass in response to high-fat diet and atherogenic index in mammals. Contributions of altered nutrient uptake, adipose tissue function and/or the intestinal microbiota with the ability of helminths to alter metabolic status play a pivotal role in increased metabolism rate and may lead to wasting and even stunting formation.

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Conclusion: Helminth drives the type 2 immunity and activates its cell line which is responsible for metabolic shifting and reprogramming.

Keywords: Biochemical; stunting; soil transmitted helminths; tropical disease.

1. INTRODUCTION

Metabolism is the set of life-sustaining biochemical reactions in living organisms, specifically taking place at the level of cells; its main business is to change food into energy [1]. This energy, specifically ATP, is the currency of energy among cells [2] to accomplish every aspect in living organism, from simple motoric activity [3] to complex cognitive-intelligentsia [4] even up to sophisticated bodily growth [5]. Specific key signaling proteins in the body control the chemical reactions of metabolism by responding not just to the existence of nutrients or metabolites but also to other growth signals; that means choreographing the control of cellular metabolic processes [6].

Unfortunately, this wonderful metabolism blessing could be affected by several conditions, one of them is the darling of a tropical disease called chronic intestinal parasitic infection (specifically helminth) [7], especially when it happens in vulnerable subpopulations such as pregnant women [8] and can cause metabolic shifting [9]. Metabolic shifting evolved due to the periodic nature of the environment, occurs on a regular basis due to the demand-availability interplay of energy resources (food), expenditures (growth, infection etc.), and depots (excessive food intake), all of which have a periodic nature due to the environment's circadian rhythmicity [9].

Metabolic shifting is actually the hallmark of most common diseases and the quest for the underlying unity of its pathogenesis is crucial [10]. Chronic metabolic shifting together with other deteriorating conditions such as persistent exposure to infection, can cause a catastrophe vicious circle in children called stunting [11,12] and this became the aim of this mini-review.

2. STUNTING AT A GLANCE

Epidemiologically, eventhough there has been a reduction in child stunting rates from 40% in 1990 to 23% in 2016, 155 million children worldwide still suffer from stunted growth, mostly in Africa, South Asia, and Southeast Asia, stunting is still a great neglected major health problem, especially in underdeveloped countries [12]. Stunting always related to restriction to food intake and in combination with prolonged infection [7-11].

A condition of chronic or recurring deficiency of correct nutritious foods, both in quantity and quality, for mothers [8] and children during the whole prenatal and postnatal periods [12-14] subsidizes to the formation of stunting [7]. Children who are stunted (length-for-age Z-score<-2) are at greater risk of infectious morbidity and mortality [12].

The most well-accepted pathway to the existence of stunting is a complex ‘vicious cycle’ between long term nutritional deprivation [13] and chronic-persistent infection [14], which is progressing negatively to fence in microbiota dysbiosis of the intestine [15] which causes the disappearance of intestinal immune cell function [16], and triggers the local intestinal inflammation [17,18], and when it happens in the specific portion of intestinal walls defined as leaky gut, [19] a weakening of the intestinal walls which in turn allows bacteria and toxins to be released into the bloodstream. It then will trigger chronic, full body inflammation or systemic inflammatory responses [20]. Adjacent to energetic, hormonal, and metabolic sequela, anemia is also on numerous occasion experienced as co-morbid condition of stunting [21]. Furthermore, anemia found in mother [8,22] and/or child [23] may be overlapping causing stunting.

Common chronic persistent infection among children is caused by intestinal parasites [7], mostly the soil transmitted helminths, or STH [30], which are parasitic nematode worms that live in the human intestine [31]. The three most common STH infecting humans are: round worm *Ascaris lumbricoides*, whip worm *Trichuris trichiura* and hookworm *Ancylostoma duodenale* and *Necator americanus*. They easily disseminate through soil or water contaminated by human stool that contains the parasite larvae [30,31]. STH infections are considered the great neglected tropical diseases or NTDs [32].

3. HOW INTESTINAL PARASITIC INFECTION CONTRIBUTES TO STUNTING

In the intestine, parasites occupy the same niche as bacteria, members of the normal microbiota [24]. The coming of new comer intestinal parasites can disrupt the normal balance of the gut microbiota [24,25] and can open the door for other bodily derangement [26]. The two-way relationship between intestinal parasites and the microbiota [17, 27], sometime it is already happening in very early life just as revealed by Hakizimana et al [28], and their combined reciprocally strengthened effects [14], could play a key role in stunting [12-14,17,23]. Epigenetic regulation of gene expression in children at risk of stunting [29] may link parasitic infections and poor intestinal health and function [14-20] since very early life and may lead to stunting formation [33].

The normal gut microbiome accommodates all good bacteria [34], specific fungi [35], protozoa which are sometimes classified as neglected gut microbiomes [36], the less common reported archaea [37], and even an abundance of viruses [37]- these are all well-function biomes [38] that reside in and along the gastrointestinal tract, especially in the intestine [39] and may occupy their milieu commensally [40]. The composition of the gut microbiota is probably the result of a process involving ecological memory, and not just simple host-based filtering [41]. Its composition is always in a dynamic and fluctuant state [42] and, probably, with a double face, favorable or detrimental to the host [43].

The gut microbiome plays important roles in (1) the process of metabolism - i.e., the metabolism of nutrients, such as indigestible polysaccharides, lipids, vitamins, and AAs [44], (2) gut epithelial well-being [34,37,39,40], and (3) controlling the systemic innate [45] and adaptive [46] immune responses, even to the extent of promoting immune tolerance [47]. As far as is known, the human host and microbes have coevolved throughout evolutionary history in the gastrointestinal niche [48,49], and it is postulated that their closed interaction [50] has adapted to exert dynamic influences on each other [51]. Helminth infection increases the host's microbiome diversity, together with its richness [52]. Ongoing helminth infection has been associated with the suppression of bodily allergies reactions [53] and also a converted susceptibility to certain microbial infections due to the shift in the host's immune response [54].

Study revealed that active and chronic helminth infections can protect against allergic ailment by an active regulatory process [55] by the aid of its intense modulation of the specific host immune system dictated by expanding repertoire of parasite effector molecules [56] (e.g., Anti-inflammatory protein-1, a family member of tissue inhibitor of metalloprotease (TIMP)-like proteins secreted by *N. americanus,* which act as suppression in TNBS colitis model: promotes expression of colon IL-10, TGF-β, and TSLP and the accumulation of Treg cells in the colon and Anti-inflammatory protein-2 also secreted by *N. americanus*, a family member of TIMP-like proteins which causes suppression in model of allergic airway inflammation via Treg cell induction and suppression of T cell proliferation in cells from house dust mite (HDM)-allergic patients), therefore leading to a systemic T-cell hyporesponsiveness to parasite antigen [57], which is triggered by the induction of a complex regulatory network initiated by the regulatory cytokine IL-10 [58,59] and TGF-β family [57]. Basically, helminth-induced immunoregulation occurs through the induction of regulatory T cells [60] and or Th2-type cells [61], and this plays a role for Treg in limiting inflammation-induced pathology following helminth infection [60]. An increased proportion and expansion of adaptive Treg cells is also reported by Santos et al in Brazil [62] which reported *Ascaris lumbricoides* coinfection with active tuberculosis actually reduces infected tissue damage by reducing IL-6 levels without altering the clinical progression of pulmonary tuberculosis or Th1/Th2/Th17 cytokine profile.

Although, significant complex environmental exposure on individual members of the community causing dynamic variation regarding regular daily diet [63], personal hygiene [64], environmental sanitation conditions which contribute to ecologically based natural selection [65], helminth related species and burden which infected [66] and so many other factors that make it strenuous to accomplish consensus regarding the consequences of helminths on the gut microbiome reciprocally. Inconsistent associations between active helminth infection and its related parameters such as species abundance, diversity and taxonomic plethora commonly used to profile the microbiome actually already revealed by previous literature review studies. These inconsistencies advocate

that factors such as host genetics (e.g., in relation to the host's gender and genotype) [67], nutrition [68], the history of exposure to anthelmintic or other treatment [69] and the condition of co-infections [70] may also exert influence on the reciprocal effects of helminths on the microbiome or the microbiome on helminths. This interesting pile of knowledge bolsters up the need for more extensive study, perhaps with meta-analyses, to accommodate all the data with the approach of cross-study and cross-population in order to get better understanding regarding the role of dynamic interaction between the host's microbiome, the parasite and the environment. In the next section, we are going to link this interaction with the metabolic shifting experienced by individuals who are which chronically infested with parasite.

4. METABOLIC SHIFTING IN INDIVIDUAL INFESTATED WITH CHRONIC PARASITIC DISEASE

Here, we provide a comprehensive review regarding this sub-topic subtopic. Even during earliest exhibition to the invasion of parasites, hosts can establish behavioral and or physiological responses [72]. Those responses may occur without the host realizing or fully aware about it. The tendency of chronicity regarding parasitic infection and inability to combat innumerable species of parasitic helminths that become co-evolved with their preference hosts over the history of mankind proposes that certain mammals have accustomed mechanisms which tolerate this specific infectious disease [73]. That conditions expose the host to certain metabolic costs [71,74]. Ongoing inflammatory and immune responses are associated with dramatic shifts in tissue metabolism. These changes include local and persistent depletion of important nutrients [13], increased oxygen consumption [4], and the generation of large quantities of reactive nitrogen and oxygen intermediates [20]. Such enormous shifts in tissue metabolism derive, at least in part, from profound recruitment of inflammatory cell types, particularly myeloid cells, such as neutrophils (polymorphonuclear leukocytes [PMNs]) and monocytes [44]. In reality, the vast majority of inflammatory cells are directed to, as opposed to resident at, the region infected and suffer inflammatory lesions [18]. "By stark contrast, adaptive immune responses are characterized by high rates of local T and B cell proliferation and have significantly different metabolic demands. Detrimental effects of parasitism on host fitness are frequently attributed to parasite-associated demands to host's energy" [74].

Unfortunately, few studies have measured these costs directly. Hence, little is known about metabolic costs arising from parasite exposure. Furthermore, no one has yet measured whether and how previous infection history modulates metabolic responses to parasite exposure.

"In case of chronic (intestinal) helminth infection, there is an interplay of type 2 immunity, helminth infection and the microbiota in regulating the host's metabolism" [75]. During ongoing helminth infection, type 2 immunity is required to limit worm burdens and to promote the timely repair of the damage caused by tissue migrating larval stages of the parasite. With the involvement of Type 2 immunity, which has recently been noticed as a crucial player in the host's metabolic status [76], with innumerable studies analyzing the role of type 2 immune cells within adipose tissue [77,78].

Metabolic dysfunction which occur during active helminth infection is repeatedly designated as a sustained low-grade or chronic inflammatory state within the infected part of the tissues [79], and type 2 immunity may simplify a return to the condition of metabolic homeostasis, as part of the host protective function [80]. Ideally, the immune response is designed to the specific milieu in which it takes place [12,16]. "Immune cells have the special ability to sense and adapt to fluctuation in their surroundings, and it is now getting more noticed that in addition to cytokines made by stromal and epithelial cells, metabolic cues provide key adaptation signals. Changes in immune cell activation states are linked to changes in cellular metabolism that support its function" [81]. "Furthermore, metabolites themselves can signal between as well as within cells" [40,79,81]. "Metabolic regulation relates to type 2 immunity firstly by considering specifics of metabolism within type 2 immune cells and secondly by stressing how type 2 immune cells are integrated more broadly into the metabolism of the organism as a whole" [81].

A complex network of type 2 resident cells including The anti-inflammatory M2 macrophages [82], eosinophils [83] and group 2 innate lymphoid cells (ILC2s) [84] has been properly identified within adipose tissue. In spite of the fact that the exact effector cells in this

equilibrium have not been intelligibly recognized, any change of the type 2 microenvironment resulted in a shifted metabolic state [85]. This shifted metabolic state of the host sometimes also called metabolic reprogramming [9,10,85-87].

The characterization of metabolic reprogramming toward glycolysis, which favors immune cell activation and its effector, is commonly seen in sepsis [86,87]. Their functional implications in anti-inflammatory [88], immune regulation [89] and later pro-inflammatory [20] responses are actually important built in features to survive from catastrophic infection. In the case of helminth parasites, they are complex metazoans that belong to different taxonomic families but collectively share the ability to downregulate the host immune response directed toward themselves (parasite-specific immunoregulation). During long-standing chronic infection, these helminths appear to have the ability to dictate its host by way of suppress immune responses to bystander pathogens/antigens and atopic, autoimmune, and metabolic disorders.

At least, there are two major features of metabolic reprogramming in inflammatory condition, in innate and as well as in adaptive immune cells, namely as follows:

1) Energy production and biosynthesis reprogramming, including increased glycolysis and decreased oxidative phosphorylation, in order to secure faster ATP production and biosynthesis for defense response and damage repair, and
2) Epigenetic reprogramming, including enhanced histone acetylation and suppressed DNA methylation, due to altered accessibility of acetyl/methyl group donor and metabolite-modulated enzymatic activity. Finally, we discuss current strategies of metabolic and epigenetic therapy in cardiovascular disease and recommend cell-specific metabolic and gene-targeted site-specific epigenetic alterations for future therapies.

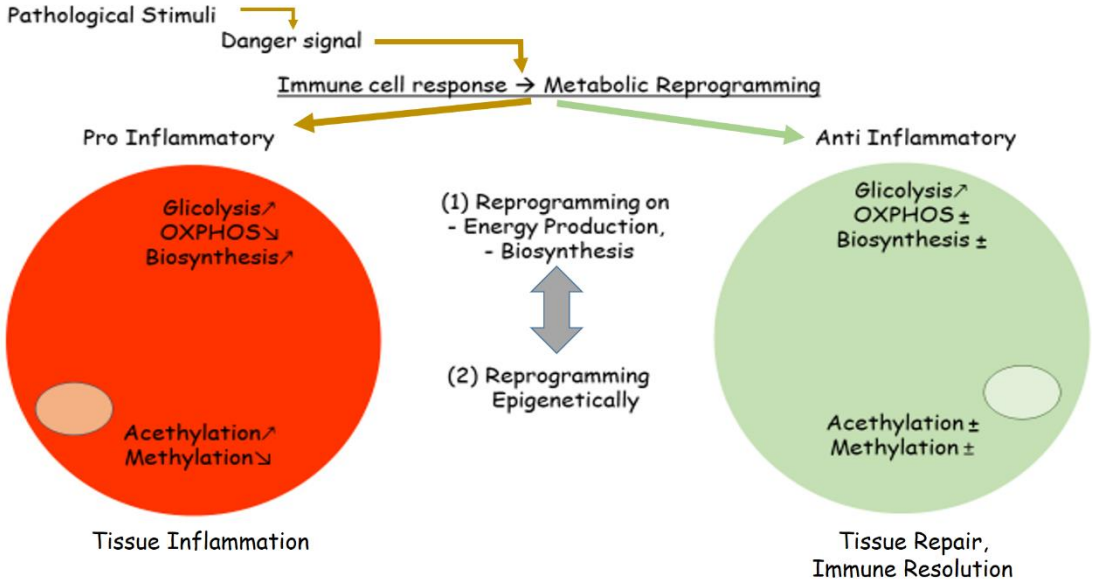

Fig. 1. Schematic steps of general interplay between immune response and metabolic reprogramming. Activation of innate immune cells by pathogen/danger-associated molecular pattern or metabolite-associated danger signal via pattern recognition receptors or metabolic sensor to facilitate the downstream signaling cascade to initiate an immune response. Metabolic reprogramming exists during this type of immune responses, in which various cellular metabolic processes in immune cells are altered to achieve an adequate function. Complex process may be involved and finally lead to a metabolic optimization in which distinct metabolic signature determines specific inflammatory or anti-inflammatory immune cell subset differentiation [86 with modification].

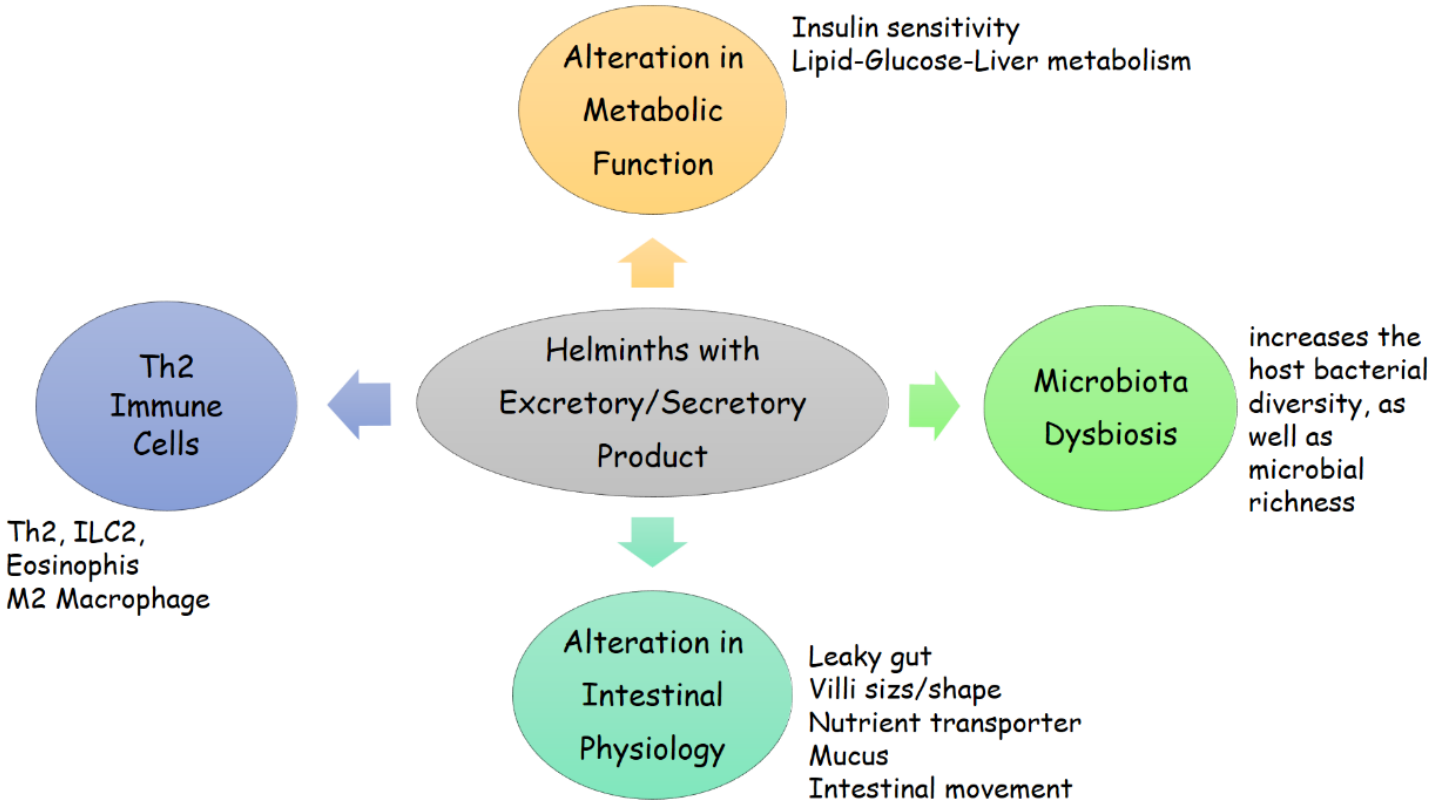

Fig. 2. Schematic representation of putative mechanisms by which helminth infection could alter the metabolic state of the host. Helminths typically elicit a type 2 immune response which has been associated with modulation of adipose tissue homeostasis, whole-body metabolic changes and changes in intestinal physiology [75, with modification]

The metabolic response of the host to helminth infection usually leads to modification in the pattern of amino acids in the body fluids [90], remodeling of the lipid metabolism, *i.e.,* a depletion of the amino acid pool, an alteration of the ketogenic pathways [79], and changes in composition of microbiota-related metabolites [54]. This profound metabolic shift also has an intense influence on the host immune status and eventually affects organs that are not directly involved in the immune response.

Helminths can make adjustments to harsh environmental conditions inside the host [91], such as utilizing anaerobic cycles such as fermentation and malate dismutation to obtain energy from carbohydrate they steal from their host [92]. Carbohydrate is an essential energy source in all mature helminths and its metabolism process is often primarily through an anaerobic cycle, even in the milieu where oxygen is abundant. Helminths also use amino acid, polyunsaturated fatty acid (PUFA), and cholesterol metabolism, a possible strategy favoring the production of immunomodulatory compounds that may influence survival in the host and evade host immunity [93].

It is clear that helminth infections can cause severe problems such as stunting in undernourished children by way of attenuation of systemic inflammation and metabolic reprogramming. Further studies need to be conducted in order to explore metabolically mediated immunosuppressive status of the vulnerable host which is infected with helminth; what species, and for how long, and also with the history of previous treatment for a chronic helminth infection.

5. CONCLUSION

Chronic metabolic shifting and reprogramming during helminth infection usually occur together with other deteriorating condition such as persistent exposure to infection and prolonged inflammation that all together can cause stunting. Type 2 immune response induced by helminth infection drives host tolerance and plays an important role in promoting tissue repair. Helminths polarizes in to M2 Macrophages and induce a metabolic shift towards reliance on oxidative phosphorylation, lipid oxidation and amino acid metabolism. Helminth-induced activation and metabolic reprogramming of macrophages underlie improvement in overall whole-body metabolism, denoted by improved insulin sensitivity, body mass in response to a high-fat diet and atherogenic index in mammals. Contributions of altered nutrient uptake, adipose tissue function and/or the intestinal microbiota with the ability of helminths to alter metabolic status play a pivotal role in increased metabolism rate and may lead to wasting and even stunting formation.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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