

Association of Hygiene Hypothesis with High prevalence of Allergy and Autoimmune Diseases: FMT industry

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Abstract—Prevalence of Allergy and Autoimmune Diseases are high in developed countries, but not in developing countries. Helminth infection were associated with lower level of allergy but the mechanism is not yet clear. In hygiene countries like UK, Japan and Korea, Fecal Microbiota Transplantation (FMT) has gained interest as novel therapy and prevention and reach to medicine industrial manufactures. This study will support it by associate Hygiene Hypothesis (HyHy) and the high prevalence of Allergy and Autoimmune Disease. Systematic review and Bayesian network analysis in EBSCO host search engine were used. Result from dynaMed Evidence Based, Point-of-care Reference e Journals: Dentistry, Medical and Nursing has describe 9 literatures support the association of Hy-hy/parasite infection with Allergy and/ or Autoimmune Diseases: 2 publications of meta-analysis are chosen and supported by 5 cross sectional, longitudinal, cause-effect design, and 2 clinical and animal trial. Conclusions: Low-middle-high income countries has a life style of Hyhy pattern support FMT industrial medicine and travelling to developing countries with broad diversity bacteria and worm in therapeutic and prevention potential, supported by sub-saharan and tropical rainforest developing countries.

Keywords— Hygiene hypothesis, allergy, autoimmune diseases, FMT industrial medicine, traveling to developing countries.

I. INTRODUCTION

A firm increase of global prevalence in allergic diseases mainly among children in the last few decades. Over the years, where several epidemiological studies have reported an inverse association between parasitic worm infections and allergies. The relationship between helminthes infection and allergies is urgent as research aims move to approach the potential of therapy and prevention in using helminths and their products for allergic disorders.¹ Using infectious disease high prevalence countries as a source of prevention and treatment of allergy and autoimmune diseases (AD). Knowledge of much references in the association of Hyhy-Allergy^{2,3,4} Molecular aspect of epitope mapping of bacteria and worm vs. lifestyle in low-middle-high income population are associated with Most of Autoimmune Diseases are costly but Fecal Microbiota Transplantation (FMT) is an effective potential therapy and vaccine.⁵ Traveling to developing countries with high biodiversity microbiota are also promising.

II. MATERIAL AND METHOD

Systematic Review and Bayesian analysis using EBSCO host DynaMed: Evidence –Based, point-of Care Reference, e-Journal: Dentistry, Medical and Nursing search engine. First, searching with CINAHL plus with developing the knowledge for the aims of study. Using the following search terms: Autoimmune Diseases, Hygiene Hypothesis, Epidemiology and AD, Atopic Sensitization, Asthma, T1D, IBS, MS, Rheumatoid Arthritis, Ulcerative Colitis, Allergic Diseases. Epidemiology AND Autoimmune Disease and UK (263), AND Japan (259). FMT are growing (4550), FMT and Meta-analysis (12), FMT and UK (34), FMT AND Japan (66). FMT industry (3), Hygiene Hypothesis AND Autoimmune Disease (117), Helminth AND Autoimmune diseases (148), Worm and Autoimmune (36), Worm and Hygiene Hypothesis (17), Epidemiology AND Meta-analysis and Rheumatoid Arthritis (27). Second step, all are screening abstract or title: excluded the not relevant and the duplicates by Bayesian analysis. Since we were interested in explanatory factors of bacteria and worm epitope sequencing are filtered. In the third step, screening full text publications, excluded since not relevant, duplicated and extracted for Table. Association of Hygiene Hypothesis or parasite infection AND Allergy/ Autoimmune Diseases. The selection was mainly performed by one reviewer and confirmed by the co-authors.

III. DISCUSSIONS

3.1 Dry and Wet climate

From clinical to molecular aspect of inflammation markers in savanna (warm and dry climate) with dormant bacteria and worm in dry season, and also in tundra (cold and dry) where no worm no bacteria in all season are searched by us. Meanwhile AD have been found in low prevalence in wet and warm (tropical rainforest) or hot and humid (sub-Sahara) countries, whereas allergy and AD are epidemic in clean countries. Dormant bacteria in dry season are specific physics-chemistry antigens and broad spectrum of variable microbiota implies rich of epitope of protein from known FMT. Figure 1 of Flowchart and Table 1 showed the association of Hygiene Hypothesis with allergy and AD.^{1-2, 4-11}

TABLE 1
DESCRIPTION OF IDENTIFIED 9 LITERATURES ON HYGIENE HYPOTHESIS(WORM-BACTERIA)-
ALLERGY/AUTOIMMUNE DISEASES

Study	Design	Population	Hygiene Hypothesis autoimmune measure	Epitope / synthetic vaccine measure
Figueiredo 2013	Comparison of high vs. low infection	Environmental condition in Latin American	Aeroallergen	Immunologic phenotypes, atopy, asthma
Obeng 2014	Cross-sectional	1385 Ghanaian Schoolchildren	Schistosome infection	Mite Atopy but not wheeze & asthma
Hamid 2011	A longitudinal study	Semi urban and rural areas of Flores, Indonesia	Intestinal helminth infections	Allergy
Xu 2015	Randomized Controlled Trial (RCT)	Metabolic syndrome subjects	Fecal Microbiota Transplantation	Beyond intestinal disorders
Lopez-Isac 2016	Meta-analysis	Meta-genome-wide association (meta-GWAS)	Systemic Sclerosis (SSc) and Rheumatoid Arthritis (RA)	Top single-nucleotide polymorphism
Colman 2014	Systematic review and Meta-analysis	18 studies of FMT primary therapeutic agent for 122 pts with 79 ulcerative colitis, 39 Crohn's disease, 4 IBD	Clinical remission and/or mucosal healing	IBS as autoimmune disease
Puentes F 2016	Animal model of autoimmune disease	Tolerogenic potential of fusion protein in 10 transgenic mouse model	Parasite proteins containing repeats are essential invasion ligands	Ability to evade the host immune system
Ajendra 2016	Experimental	NOD mice after insulinitis started in T1D process	Inflammation of the pancreatic islets	Helminth antigens as a new potential therapeutic approach against AD
Lagier 2014	Review	Longitudinal CT of Recurrent CDI patients	FMT frozen, antigens	Extensive use and wide industrialization of FMT against AD

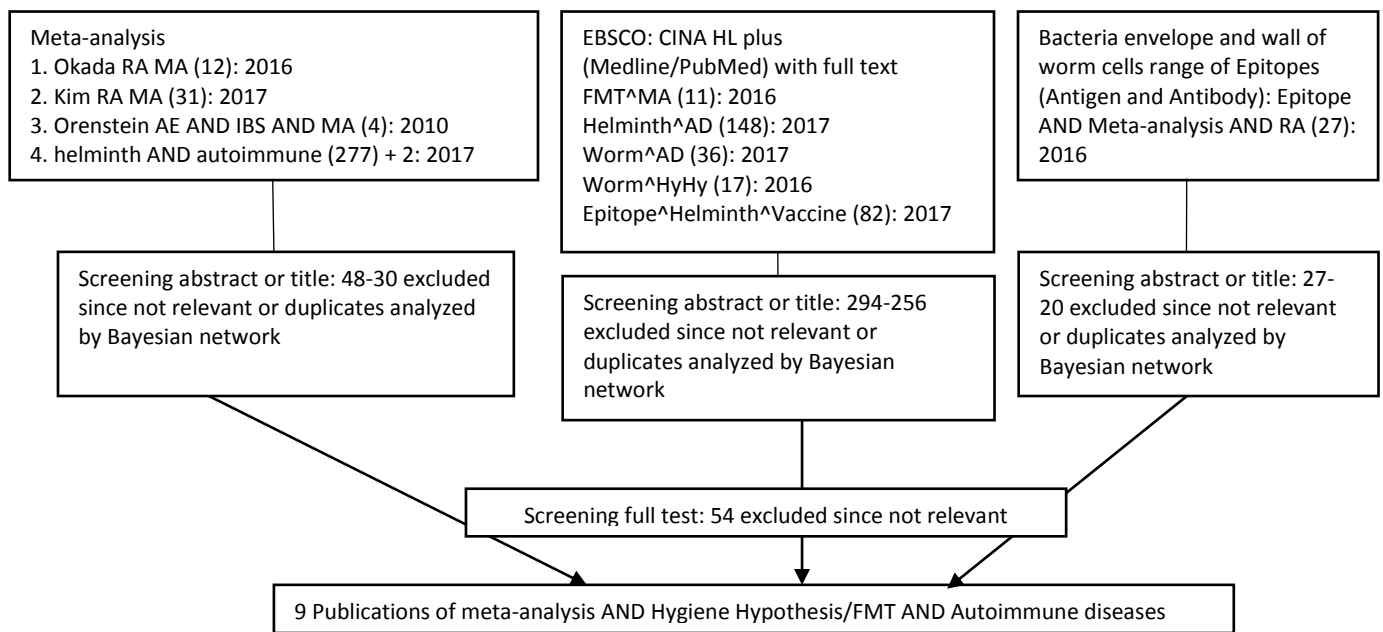


FIGURE 1. FLOWCHART OF THE 9 IDENTIFIED LITERATURE: 2 META-ANALYSIS, 2 REVIEW, 3 CROSS SECTIONAL, LONGITUDINAL, CAUSE-EFFECT DESIGN, 2 EXPERIMENTAL (ANIMAL/ AHUMAN) WHICH ASSOCIATED HYGIENE HYPOTHESIS/PARASITE INFECTION WITH ALLERGY AND AUTOIMMUNE DISEASES

Improved hygiene and little infections in childhood influence the development of allergic and autoimmune diseases. It has been reported in Latin America (Urban Brazil),⁶ a tropical rainforest area. Lifestyle factors with microbial exposure are associated with allergy prevalence also reported in developed countries.⁷

Not only microbial exposure, helminth infections are also associated with low prevalence of allergy,^{8,11} till FMT are used as therapy in Autoimmune Diseases¹²

Including metabolic diseases.⁹ Systemic sclerosis and rheumatoid arthritis has been identified have a common susceptibility locus of gene.¹³

3.2 Proinflammatory cytokine as hygiene hypothesis marker

Parasite proteins contains repeats which induce immunosuppression and induce down-regulation of TNF- α (cytokine proinflammation) and TGF- β (cytokine profibrosis) make potential application for the treatment and prevention of autoimmune diseases.¹⁴

Entering of helminth antigens increase the protective effect stipulated by antigen-peculiar therapies and symbolizes a new approach for potential therapy against AD including T1DM.¹⁵ The use of microbiota which has been frozen facilitates transplantation, and per oral are at least as effective as other invasive methods and to keep from occurring the risk of anesthesia. The use of pills form, already test as clinical trials, will certainly be the beginning landmark for the width use and broad industrialization of fecal microbiota transplantation.¹⁰

Treatment with helminthes and worms ova mitigated the clinical symptoms of numbers autoimmune diseases in animal model and in patients. Tuftsin-PC (TPC), a novel helminth-based compound, reduced proinflammatory cytokines and induced the expression of anti-inflammatory cytokine, as well as expansion of Treg and Breg cells, also histological analysis guide to a new approach for a natural therapy for beginning rheumatoid arthritis onset, one of autoimmune diseases.¹⁶

The role of transfer of immune cells adoption in worm-influenced regulation of allergy and autoimmune diseases, was supported by animal experiments.¹⁷ The chronic diseases for families economic burden, health systems, governments and the association between national policy maker and international economic pressure and politics have a large impact on chronic diseases risk and countries ability in responding them, the potential of wet and warm climate area double burden of infectious and chronic diseases.¹⁸

3.3 Economic income and Hygiene Hypothesis

How the present of chronic conditions in certain multimorbidity patterns, which could have great burden on public health at several levels in low-, middle-, and high-income countries has been identify and describe in several countries to the advancement of preventive actions to decrease their prevalence and also give increase to new, understandable approaches for the management of these co-existing conditions.¹⁹

The association of individuals raised in hygiene environment have a higher of developing Allergy and Autoimmune Diseases was supported by random or fixed-effect meta-analyses.²⁰

IV. LIMITATION

These Systematic review has several limitation 1) Non published literature on all autoimmune diseases may limit the validity of our findings, but these inflammatory bowel diseases and rheumatoid arthritis study are a real phenomenon which is already attracted peoples from developed and clean countries with AD burden. However, we used meta-analysis with partly overlapping data bases for our literature search on bacteria and worm cell wall antigens. And we found a large number of papers fulfilling the criteria of our search in these HyHy-AD prevention and therapeutic. 2) Another potential problem in this systematic review is that studies mainly used in the searching steps are depended on the vocabulary synonyms (not find in general, but many in specific such as autoimmune diseases could be Rheumatoid arthritis, recurrent CDI, IBS, T1D, atopic sensitization, asthma etc.) but not in Lupus Erythematosus. Different chances changes choices used give different results may be misleading. We intended to manage this problem in an additional work, by dividing the using chosen specific to generic into 2 broad categories: prevention and therapeutic findings.

V. SUMMARY

Epitope of FMT, bacteria, wall of worm are all rich of ranges epitopes and could be present in therapeutic a prevention potential. These epidemiological studies from developing/ tropical rainforest area countries, present to hygiene developed countries is similarly paralleled with low-middle- high- income population, vaccination and therapeutic fighting against autoimmune diseases. Hygiene hypothesis / FMT has association with novel treatment for Allergy and Autoimmune Diseases. Further knowledge and education to policy maker and global politic doer from local to global will support the industries in FMT.

VI. CONCLUSION

Low-middle-high income countries has a life style of Hygiene hypothesis. The low- and middle economic income in development countries have similar pattern with population in developing countries, which support FMT industrial medicine and travelling to developing countries. Broad diversity bacteria and worm in therapeutic and prevention potential, supported by sub-saharan and tropical rainforest developing countries.

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REFERENCES

- [1] Amoah AS, Boakye DA, van Ree R, Yazdanbakhsh M. Parasitic worms and allergies in childhood: insights from population studies 2008-2013. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol* 2014;25(3):208-17.
- [2] 2. Shunsheng Han C. A specific hygiene hypothesis. *Med Hypotheses* 2016;93:146-9.
- [3] 3. Yang J-Q, Zhou Y, Singh RR. Effects of Invariant NKT Cells on Parasite Infections and Hygiene Hypothesis. *J Immunol Res* 2016;2016:2395645.
- [4] 4. Lynch SJ, Sears MR, Hancox RJ. Thumb-Sucking, Nail-Biting, and Atopic Sensitization, Asthma, and Hay Fever. *Pediatrics* 2016;138(2).
- [5] 5. Varier RU, Biltaji E, Smith KJ, Roberts MS, Jensen MK, LaFleur J, et al. Cost-effectiveness analysis of treatment strategies for initial *Clostridium difficile* infection. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2014;20(12):1343-51.

- [6] 6. Figueiredo CA, Amorim LD, Alcantara-Neves NM, Matos SMA, Cooper PJ, Rodrigues LC, et al. Environmental conditions, immunologic phenotypes, atopy, and asthma: new evidence of how the hygiene hypothesis operates in Latin America. *J Allergy Clin Immunol* 2013;131(4):1064.
- [7] 7. Hesselmar B, Hicke-Roberts A, Wennergren G. Allergy in Children in Hand Versus Machine Dishwashing. *Pediatrics* 2015;135(3):e590-7.
- [8] 8. Obeng BB, Amoah AS, Larbi IA, de Souza DK, Uh H-W, Fernández-Rivas M, et al. Schistosome infection is negatively associated with mite atopy, but not wheeze and asthma in Ghanaian schoolchildren. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2014;44(7):965-75.
- [9] 9. Xu M-Q, Cao H-L, Wang W-Q, Wang S, Cao X-C, Yan F, et al. Fecal microbiota transplantation broadening its application beyond intestinal disorders. *World J Gastroenterol* 2015;21(1):102-11.
- [10] 10. Lagier J-C. Faecal microbiota transplantation: from practice to legislation before considering industrialization. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2014;20(11):1112-8.
- [11] 11. Hamid F, Wiria AE, Wammes LJ, Kaiser MM, Lell B, Ariawan I, et al. A longitudinal study of allergy and intestinal helminth infections in semi urban and rural areas of Flores, Indonesia (ImmunoSPIN Study). *BMC Infect Dis* 2011;11:83.
- [12] 12. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;8(12):1569-81.
- [13] 13. López-Isac E, Martín J-E, Assassi S, Simeón CP, Carreira P, Ortego-Centeno N, et al. Brief Report: IRF4 Newly Identified as a Common Susceptibility Locus for Systemic Sclerosis and Rheumatoid Arthritis in a Cross-Disease Meta-Analysis of Genome-Wide Association Studies. *Arthritis Rheumatol (Hoboken, NJ)* 2016;68(9):2338-44.
- [14] 14. Puentes F, Dickhaut K, Hofstätter M, Pfeil J, Lauer U, Hamann A, et al. Immune Modulation and Prevention of Autoimmune Disease by Repeated Sequences from Parasites Linked to Self Antigens. *J Neuroimmune Pharmacol Off J Soc Neuroimmune Pharmacol* 2016;
- [15] 15. Ajendra J, Berbudi A, Hoerauf A, Hübner MP. Combination of worm antigen and proinsulin prevents type 1 diabetes in NOD mice after the onset of insulinitis. *Clin Immunol* 2016;164:119-22.
- [16] 16. Bashi T, Shovman O, Fridkin M, Volkov A, Barshack I, Blank M, et al. Novel therapeutic compound tuftsin-phosphorylcholine attenuates collagen-induced arthritis. *Clin Exp Immunol* 2016;184(1):19-28.
- [17] 17. Ding Y, Zhou R, Yang X, Zhang L. [The Role of Adoptive Transfer of Immune Cells in Helminth- induced Regulation of Allergy and Autoimmune Diseases]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 2015;33(4):290-4.
- [18] 18. de-Graft Aikins A, Unwin N, Agyemang C, Allotey P, Campbell C, Arhinful D. Tackling Africa's chronic disease burden: from the local to the global. *Global Health* 2010 19;6:5.
- [19] 19. Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. *J Gerontol A Biol Sci Med Sci* 2016;71(2):205-14.
- [20] 20. Cholapranee A, Ananthakrishnan AN. Environmental Hygiene and Risk of Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2016;22(9):2191-9.