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Potential of Fecal Microbiota Transplant in Treatment of Alopecia

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Abstract

Alopecia, a skin disease, with a global population occurrence of 0.1%-0.2% results in loss of hair from scalp & elsewhere on the body. Hair follicles, the basic structure that surrounds the root & strand of hair, are considered to be a region of immune privilege. Onset of Alopecia is triggered by collapse of immune privilege driven by autoimmune attack on hair follicles. This is supported by clinical evidence which classifies Alopecia as an autoimmune disorder. Recent studies have demonstrated that Alopecia is connected with a number of other disorders such as Cardiovascular Diseases, Rheumatoid Arthritis & more. It has been found that Gut microbiota plays a key role in immune system responses in Alopecia. Fecal Microbiota Transplant(FMT), which has been recently approved by FDA to treat clostridium difficile infection, may hold answers to cure this autoimmune disorder.This chapter unravels the potential of gut microbiota & FMT to cure Alopecia.

Keywords

Alopecia Areata, Androgenic Alopecia, Patchy Alopecia, Alopecia Totalis, Alopecia Uni- versalis, Alopecia Ophiasis, Alopecia Sisaipho, Acute Diffuse and total Alopecia, Hair Follicle, Gut Microbiota, Gut Dysbiosis, Clostridium Difficile, Fecal Microbiota Transplant, Hair Growth, Oxidative Stress,Clostridium Difficile Infection, Atopic Dermatitis, Rheumatoid Arthritis, Celiac Disease, Anxiety, Depression, Crohn's Disease, Autoimmune Disease, Leaky Gut

Introduction

Humans come into being from their mother's womb in a sterile environment. While passing through the birth canal, the child gets exposed to the mother's microbiome. Immediately after, Human milk oligosaccharides (HMO) coming from mother’s breast milk feeds the beneficial bacteria acquired by the child during birth, enabling them to kick out harmful bugs. Gradually when children turn 5, their microbiome attains adult-like maturity & microbiome colonizes skin, gut, oral cavity, nasal, gentle & respiratory tract surfaces covered by epithelia. This “ microbiome” is nothing, but genomes of various symbiotic, commensal & pathogenic microbes living on & inside the human body which includes bacteria, fungi, yeast, viruses, protozoa & archaea. There are around 100 trillion such single & multicellular microorganisms living inside the body encoding 3.3 million genes, 100 folds more than human genes. This is the reason microbiota is also referred to as “ Second Human Genome”. Amongst various body organs, the gut or large intestine has the largest colonization of these tiny, invisible army of microbes. The composition of microbes is influenced by age, nutrition, gender & lifestyle.

As discussed above, the development of healthy, highly diverse & beneficial microbiota occur during early period of birth-infancy, thereby influencing health state & right immune response during adulthood. Gut Dysbiosis during early life entering the baby's gut either through the mother's microbiome or wrong dietary choices have a negative impact on their health in future years.

After the microbiome attains adult-like maturity, the dietary & lifestyle choices have the biggest impact on gut microbiota-human host interaction. Although gut microbiota includes bacteria, viruses, fungi, yeast, protozoa & archaea, the bacterial population is the highest, most studied & maintains symbiotic relationship with the human host.

Besides maintaining gastrointestinal homeostasis, microbes living in the gut are connected with various functions of host biology. Beneficial microorganisms living in the gut play a key role in producing various vitamins, minerals, antioxidants & short chain fatty acids, production of hormones & neurotransmitters, neutralizing pathogens, communicating with the brain,and maintaining immune homeostasis providing anti infection support, lipid & glucose metabolism & improving satiety.

Highly diverse microbiota play a key role in wellness of the human host & is connected with host metabolism, growth & immune function of the host. Manipulation of activities, functions & behavior of highly diverse gut microbiota has a far reaching impact on human host health. Gut Microbial Imbalance

Through cell to cell signaling & release of antimicrobial peptides regulating activities of nearby bacterial groups for their persistence in the human host, microbial ecosystem strikes a homeostasis. These gut microbes, through various secondary molecules & compounds, as discussed above, interact with the human host in a symbiotic or harmful way, thereby altering

both human & microbial gene expression. Underexpression or Overexpression of these genes give rise to development of infectious & various preventable chronic diseases respectively. Specifically, gut microbiota impact influences intestinal integrity & barrier strength, thereby impacting immune response which has been connected with inflammatory & autoimmune diseases.

Secondary metabolites- various molecules & compounds produced as a result of microbial metabolism of food/diet host consumes can trigger metabolic, digestive & immune pathways, thereby either having beneficial or pathogenic impact on host health. These 100 trillion microorganisms, arising out of 1000 different species with multiple strains, have defined redundant or competing functions to thrive either through working in symbiotic relationships or waging a war against each other depending upon the gut environment created by the host through their nutrition & lifestyle choices.

An imbalanced gut microbiota results in release of harmful secondary metabolites, bioactive compounds or toxins which makes the immune system trigger inflammation to neutralize these pathogens. Overtime, prolonged release of these toxins result in low grade chronic inflammation, leading to onset & progression of various chronic illnesses such as immune, metabolic, neurological & cardiovascular diseases. Modifications & improving diversity of gut microbiome through the right set of therapeutic interventions may improve clinical & health outcomes across highly diverse demographic backgrounds.

Gut Microbiota & Autoimmune Diseases

Autoimmune diseases are conditions which occur when an individual's immune system runs rampant & starts attacking its own healthy tissues & immune cells. Given the fact that 80% of the immune system resides in the gastrointestinal tract, gut dysbiosis & autoimmune diseases are linked. In a number of studies involving animal & human models, gut dysbiosis was found to be connected with onset & development of autoimmune diseases.

The connection between gut microbial imbalance & autoimmune diseases is attributed to multiple biological mechanisms dysregulations impacting functioning of the immune system.This Dysregulation includes inability to differentiate between immune cells & foreign particles attributing to similar molecular composition. Also referred as Gut dysbiosis, an imbalance of gut microbes can compromise the gut lining & make the gut lining permeable. This allows food particles & bacteria to pass through gut lining that it shouldn't. Consequently the immune cells get into action & activates antigen dendritic cells, thereby leading to pro-inflammatory cytokine production. This further disrupts the balance between TH17 cells & T regulatory cells(Tregs). The immune system is unable to differentiate between its own cells & foreign particles, attributed to similarity in molecular composition, also referred as molecular mimicry. As a result, auto reactive T cells & B cells that further secrete antibodies.These antibodies start attacking immune cells, enzymes or body organs.This results in chronic inflammation, immune system dysregulation & leads to autoimmune diseases.

There is abundant evidence that suggests the role of gut dysbiosis may be involved in further amplifying progression of disease in patients suffering from autoimmune diseases. The possible mode of this connection between alteration in gut microbiota & autoimmune diseases is molecular mimicry, as discussed above, host's immune response caused by gut dysbiosis & intestinal permeability. Alterations in gut microbiota can interfere with immune sensing & differentiating between pathogens & immune cells & tissues, leading to autoimmune diseases.

Patients with autoimmune diseases experience organ dysfunction, life long symptoms & chronic health conditions, low productivity at work, anxiety & depression, skin issues, hair loss & exorbitant expenses on immune suppressants & steroids. This is because patients with autoimmunity have leaky gut which leads to pathogenic immune responses, thereby making disease more severe.

In recent years, a number of studies have shown that regulating the activities of gut microbiota & promoting production of beneficial secondary metabolites through multiple approaches such as antimicrobial solutions, antibiotics, Fecal Microbiota Transplant(FMT) & other therapeutics, can help overcome multiple chronic health conditions including autoimmune disorders such as Alopecia However, the effectiveness of antibiotics & other drugs depends upon gut microbiome composition. On the flipside, some antibiotics have side effects with detrimental impact on activities of gut microbiome composition further creating gut microbial imbalance.

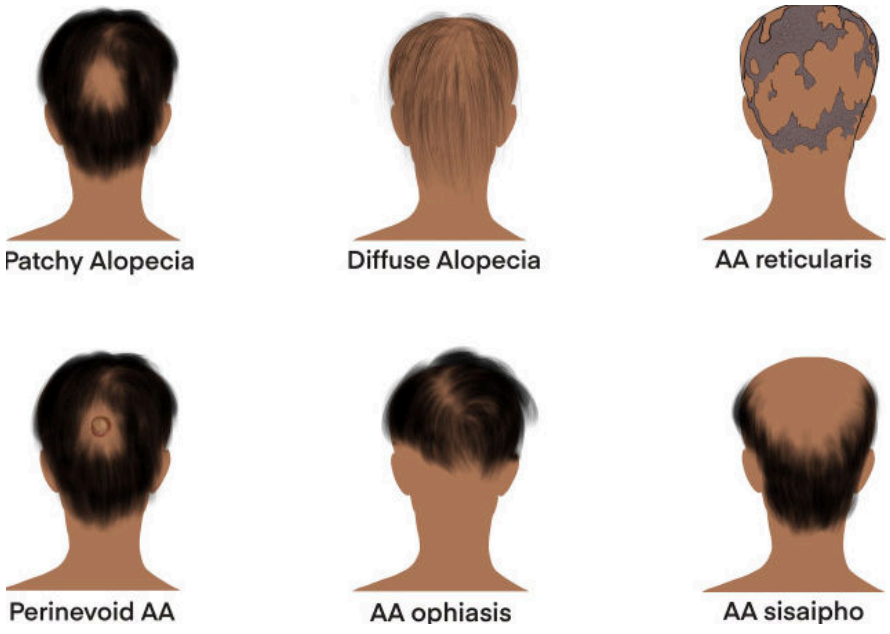
There is growing evidence which suggests that gut dysbiosis induced chronic inflammation leads to onset & progression of number of autoimmune diseases including Rheumatoid Arthritis, Type 1 Diabetes, Hashimoto's thyroiditis, Grave's disease, Multiple Sclerosis, Alopecia & more. The following section discusses the role of gut dysbiosis in development of Alopecia.

Alopecia- The most prevalent autoimmune disease

Alopecia is one of the most prevalent autoimmune diseases with prevalence of 1 in 1000 people with lifetime risk of around 2 percent[10] which creates a high healthcare burden[11]. There is a growing concern for treatment of Alopecia since no evidence based treatment & cure exist for this autoimmune disorder. Recent evidence suggests that Alopecia, specifically Alopecia Areata is connected with many types of diseases such as atopic diseases, major depression disorders, rheumatoid arthritis, psoriasis, cardiovascular diseases & more.

Alopecia is an autoimmune disease of the hair follicle that causes non-scarring hair loss. Alopecia Areata is the second leading cause of non scarring hair loss which means that there is preservation not destruction of hair follicle.The condition associated with this disease includes smooth patches on scalp, but may also impact other hair bearing areas such as eyebrows, eyelashes & beard. The development of Alopecia Areata may be erratic and/or patients may experience a period of remission & recurrences[12]. Multiple subtypes of Alopecia Areata have been defined, the most frequent occurring being patchy alopecia. Other forms include Alopecia totalis which refers to total loss of scalp & Alopecia Universalis, which means total loss of body hair & scalp. Another one is Alopecia Ophiasis which appears in an area from top of ear onwards[13]. Alopecia Sisaipho is a phenotype with scalp loss in the central part. In a number of cases, Alopecia Areata starts with a patch but evolves into Alopecia Totalis, Universalis or Ophiasis.

Fig 1[29]: **Clinical classification of Alopecia Areata variants**



The regular hair loss is a key indicator/ prognostic factor of Alopecia Areata. Loss of hair in areas other than scalp depicts a poor prognostic factor. Changes in nails are connected with severe forms of Alopecia-Alopecia Totalis & Alopecia Universalis.

Alopecia Areata is also associated with several serious disease conditions such as metabolic syndrome, hyperinsulinemia, iron deficiency, underactive thyroid (hypothyroidism) & mental health issues such as anxiety, depression & more. Besides, people suffering from Alopecia Areata also experience chronic issues such as Psoriasis, rheumatoid arthritis & other autoimmune diseases[14]. Around 12%-16% of people suffering from Alopecia Areata develop an autoimmune disease[15].

Table 1[28]:Autoimmune Diseases associated with Alopecia Areata

Autoimmune disease	References
Hashimoto thyroiditis	[21]
Vitiligo	[22]
Systemic lupus erythematosus	[23]
Autoimmune thrombocytopenic purpura	[24]
Type I (insulin-dependent) diabetes	[25]
Myasthenia gravis	[26]
Celiac disease	[27]
Scleroderma	[22]
Ulcerative colitis	[22]

During the development of Alopecia Areata, the immune system triggers production of auto reactive T cells & secretes antibodies, as discussed in the previous section, thereby leading to autoimmunity & interferes with immune sensing. This results in accumulation of pro-inflammatory T cells on the hair bulb, thereby attacking hair follicles & leading to hair loss.

Autoimmune diseases are bifurcated into immune mediated diseases & autoantigen triggered diseases. Some of the autoimmune diseases such as celiac diseases & rheumatoid arthritis are triggered by antigenic mimicry while most of other autoimmune diseases are immune system mediated. Diseases such as Alopecia Areata & Psoriasis do not have any autoantigen associated with them.

In a recent primary research involving direct interviews via video call conducted by the author, it was found that patients suffering from Alopecia Areata first developed Hyperthyroidism which later developed into Hashimotos. This research depicts the association of autoimmune diseases with development of Alopecia. However more research on other autoimmune diseases is required to elucidate this connection.

Pathogenesis of Alopecia Areata

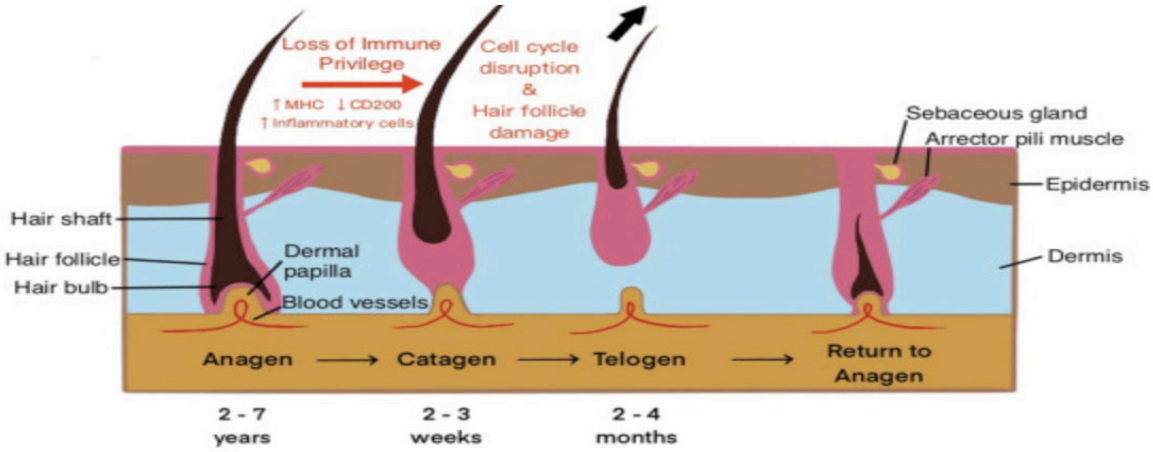
a) Hair growth cycle & hair follicle disruption

Hair follicle, hair shaft & sebaceous gland are together referred to as pilosebaceous units.The infundibulum segment is the upper portion of hair follicle which begins with the surface of epidermis & ends at sebaceous duct. Bulge, situated next to the dermis, plays a key role in the hair cycle as it nurtures stem cells that will generate transit amplifying cells during growth. The regeneration area- referred to as the bulb is composed of hair follicle matrix. Within this hair follicle, there are melanocytes which contribute towards production of hair pigment. The hair follicle epithelium consists of concentrated layers forming the outermost outer root sheath, the inner root sheath & internal hair shaft[16]. In the growth phase, matrix cells multiply that drive differentiation into transit-amplifying cells which in turn will deploy bulb & hair shaft. As nutrition supply to cells falls, the growth of the hair shaft stops. In the last two stages of the hair cycle also known as catagen which refers to controlled apoptosis of epithelial cells & telogen that refers to resting phase respectively, necessary conditions are created to start a new cycle for hair growth. During catagen phase, hair follicle regresses & involves apoptosis of small portions. Immune cells occupy space around catagen phase hair follicles. This process exposes the immune system to low levels of the hair follicle's antigens[17]. In case, the catagen regression deviates, overexpression of antigen to the immune system crosses the threshold, thereby leading to development of Alopecia Areata.

Simply put, each of the different phases of the hair follicle cycle is regulated by different cells & signaling molecules via different pathways & are essential for hair growth. If this homeostasis is impacted in any of the stages, the development & growth of hair follicle cycle is impacted. During the initial phase of the disease, inflammation is a key characteristic which triggers activities of cytotoxic T-cells, causing apoptosis of peripheral cells, thereby causing thinning of hair shaft. This inflammation causes transition from anagen to telogen phase. However since it

does not impact stem cells, the hair follicle has the capacity to regenerate if it disappears after the growth stage. However if during the Anagen phase, the hair follicle is again affected by inflammation, the hair growth cycle would be interrupted & Alopecia Areata will continue.

Fig 2[29]:**The hair growth cycle**



b) Immune Privilege & its collapse- the autoimmune response to inflammation on hair follicle

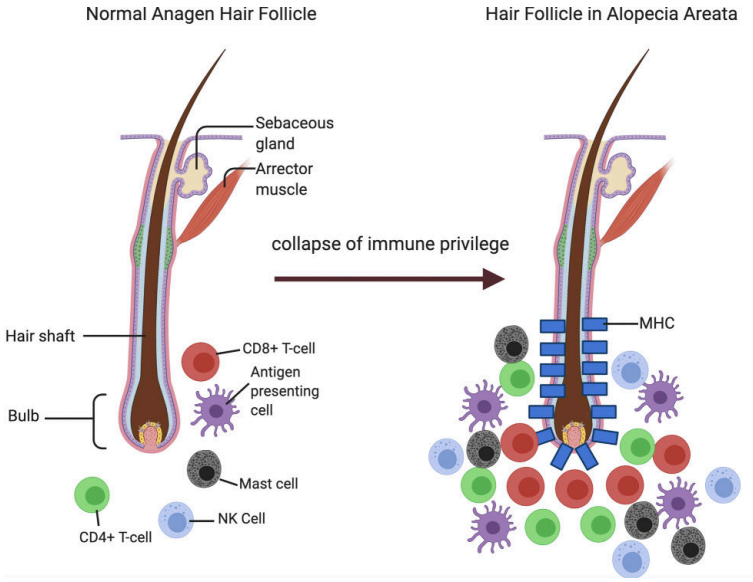
Hair follicle, whole damage by pro-inflammatory T cells results in Alopecia, enjoys immune privileges like organs such as brain, eyes, placenta[18]. Immune Privilege is a tolerance microenvironment that prevents damage of vital structures of our body from inflammation induced by pathogens & harmful metabolites released by gut microbiome. This hair follicle immune privilege is maintained during anagen phase, but lost during catagen & telogen phase. In other words, in the case of hair follicles, Immune Privilege protects stem cells & other cells that constitute its epithelium[19]. There are multiple ways to leverage Immune Privilege for protecting hair follicles. Extracellular matrix protects the hair bulb by preventing disruption by immune cells[20].

The anagen hair follicle immune privilege state is said to be maintained due to lack of major histocompatibility complex (MHC) class 1 & CD 200 in the outer root sheath. Collapse of immune privilege leads to inflammatory cells attacking hair bulbs referred to as " Swarm of bees". During development of Alopecia Areata, chronic inflammation results in crash of immune privilege & secretion of a type of cytokines- chemotactic cytokines such as IL-2 & IL-5 that leads to dystrophic anagen phase & premature launch of telogen phase. Production of these cytokines acts as chemotactics for other immune cells in the hair follicle[19]. Overexposure of autoantibodies/autoantigens during anagen phase of the hair cycle directly impacts hair follicle cycle.

Increased expression of MHC class 1 & 2 triggers recruitment of lymphocytes to the hair bulb.The fall of immune privilege leads to swarms of CD8+ T-cells, CD4+ T-cells, antigen-presenting cells, and mast cells surrounding the follicle. These immunoinflammatory

cells stop hair growth & cause damage to the hair follicle.This inflammation also leaves the stem cell component of the hair follicle, leading to hair loss that is reversible.

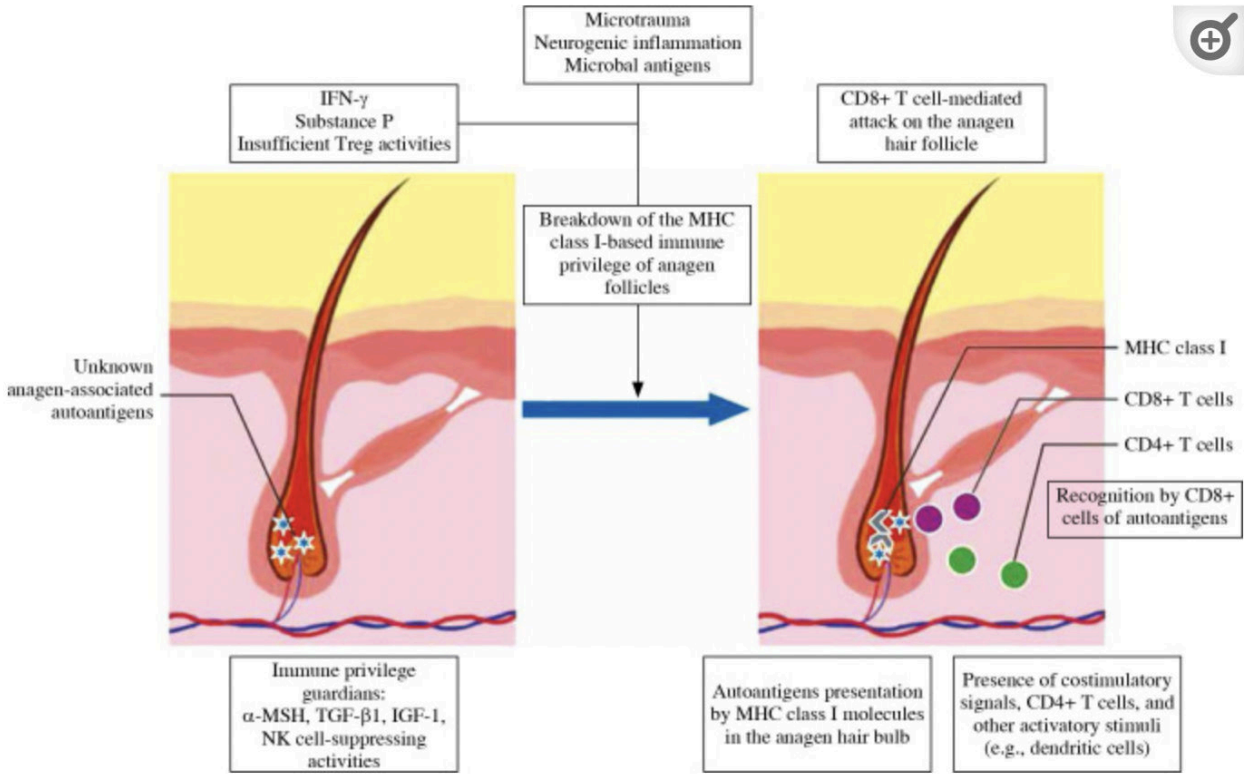
Fig3[29]: Swarm of Bees



Immunopathogenesis of Alopecia Areata[29]

In case of Alopecia Areata, Autoantigens on MHC class 1 & 2 interact with CD8+ and CD4+ T cells during immune surveillance, or in response to inflammatory signals due to toxic metabolites released by gut microbiome. Inflammatory cytokines & chemokines released by these auto reactive T cells act on hair follicle cells, making them release more cytokines & chemokines that further recruit T cells & NK cells. IFN-γ further triggers overexpression of cytokines IL-15 & chemokines in hair follicles via JAK-STAT pathway. In CD8+ T cells, IL-15 increases production of perforin and cytotoxic granzymes, also via the JAK-STAT pathway. NKG2D + NK cells and CD4+ T cells can bind with NKG2D ligands on the hair follicle, triggering further release of perforin and cytotoxic granzymes and resulting in apoptosis of hair follicle cells.

Fig4[27]


Microtrauma
Neurogenic inflammation
Microbal antigens
IFN-γ
Substance P
Insufficient Treg activities
CD8+ T cell-mediated attack on the anagen hair follicle
Breakdown of the MHC class I-based immune privilege of anagen follicles
Unknown anagen-associated autoantigens
MHC class I
CD8+ T cells
CD4+ T cells
Recognition by CD8+ cells of autoantigens
Immune privilege guardians: α-MSH, TGF-β1, IGF-1, NK cell-suppressing activities
Autoantigens presentation by MHC class I molecules in the anagen hair bulb
Presence of costimulatory signals, CD4+ T cells, and other activatory stimuli (e.g., dendritic cells)

Role of gut microbiota in development of Alopecia

Recently, a number of studies have found close association between the immunomodulatory role of gut microbiota & distant organs such as skin & hair. Specifically in the case of gut-skin axis, gut microbiota regulate functionality & composition of the innate & adaptive immune system[44] which suggest close relationship between gut dysbiosis & imbalance in skin microbiome & role of gut microbiota in onset & progression of inflammatory skin diseases. Although there is no evidence on the connection between gut dysbiosis & development of Alopecia Areata, a recent study has proposed this association[45]. As discussed in previous sections & established by author in his primary research, patients with autoimmune disease have risk of developing Alopecia Areata & vice versa[46].

Preclinical studies in non-human models have provided vital insights on the indirect relationship between gut dysbiosis & pathogenesis of Alopecia Areata[47]. An important factor in pathogenesis of Alopecia Areata is the function of T-lymphocytes Treg. Treg is said to play an important role in disease tolerance & prevention of development of autoimmune disorder[48] & are found to be in abundance in hair follicles. In a study in 2017, it was found that Treg in hair follicles promoted regeneration by increasing the abundance & differentiation of stem cells[49]. Besides, the population of Treg in Alopecia Areata Lesions is different from the healthy population. Here the role of gut microbiota becomes important. Production of Short Chain fatty acids as a result of bacteria derived metabolites from anaerobic fermentation of fiber-polysaccharides & oligosaccharides which can serve as energy substrates, impact multiple physiological & biological processes[50] & even functioning of intestinal Treg[51]. These interactions between Gut Bacteria derived Short Chain Fatty Acids(SCFA) & intestinal Treg influence peripheral tolerance processes & immune responses, thereby triggering onset & progression of autoimmune diseases such as Alopecia Areata.

A low activity level of butyrate producing bacteria and /or low consumption of foods high in polysaccharides or both can reduce the production of Short Chain Fatty Acids(SCFA). This results in gut dysbiosis & depletion of Short Chain Fatty Acids(SCFA) which directly impacts functioning of intestinal barrier & disrupts the tight epithelial junctions, thereby leading to leaky gut or intestinal permeability.

Leaky gut allows translocation & movement of commensal & pathogenic bacteria into circulation, disrupting immune system homeostasis & causing systemic inflammation.Gut dysbiosis triggered leaky gut results in inflammatory response which predisposes the host autoimmune diseases such as Alopecia Areata. In case of Alopecia, this pro-inflammatory response directly attacks the hair follicle, resulting in hair loss.

Analysis of Gut Microbiota in Alopecia Areata Patients

In the recent past, some studies using NGS of 16S rRNA sequencing of bacterial genes, have been conducted to study the gut microbiota of patients suffering from Alopecia Areata.

In a specific study involving gut microbiota of 15 patients suffering from Alopecia Universalis when compared with healthy population, it was observed that Alopecia patients had characterize increase in Erysipelotrichaceae, Lachnospiraceae and Eggerthellaceae families, and Holdemania filiformis, Parabacteroides johnsonii, Clostridiales vadin BB60 group, Bacteroides eggerthii, and Parabacteroides distasonis genre[52]. Highest diagnosis efficacy was found in P. distasonis and Clostridiales vadin BB60 group[52]. The study indicated that 25% increase in abundance of P. distasonis and Clostridiales vadin BB60 group increased risk of developing Alopecia Universalis by 9.4% & in case of Clostridiales vadin BB60 alone. by 11.4%[52]. This study provides disease signatures for development of Alopecia Universalis.

In another study, analysis of gut microbiota of 33 patients suffering from Alopecia areata & 35 healthier controls, recruited from China found that there was no differences in α-diversity In two study groups. However, on analysis of gut dysbiosis of patients having this autoimmune disease , increase in abundance of Blautia, Phyllobacterium, Dorea, Anaerostipes, Megasphaera, Collinsella, Sphingomonas, and Pseudomonas genera, and in Erysipelotrichaceae family was observed. Besides, Achromobacter, Megasphaera and Lachnospiraceae Incertae Sedis were found to be relevant biomarker for not only distinguishing between Alopecia patients & healthy population but also early detection of disease & even developing right set of therapeutic interventions[53].

The difference in biomarkers developed in both these studies indicate the importance of geographical location since both studies were conducted in geographies which had comparatively different nutrition choices[53].

In another study, study of gut microbiota of Alopecia Areata patients in the pediatric population consisting of 21 children & their siblings as a healthy population aged from 4 to 17 years was conducted using shotgun metagenomics sequencing method. As in previous 2 studies, there was no difference in α-diversity in two study groups. Besides, there was no difference in β-diversity as well. However, it was also observed that Ruminococcus bicirculans had lower abundance in Alopecia Areata patients[54]. When analyzing the functional role of gut microbiota, it was observed that 20 genes were differently expressed in case of children suffering from Alopecia compared with the healthy population[54].

In another study, it was found that oral corticosteroids also alter gut microbiota & therefore if the patient is on treatment should also be taken into cognizance[55].

These studies strongly support the role of gut dysbiosis & leaky gut driven systemic inflammation in pathogenesis of Alopecia Areata & further reinforces the role of treating & curing Alopecia using Fecal Microbiota Transplant(FMT) as fulcrum.

Role of Oxidative Stress in pathogenesis of Alopecia Areata

37 trillion cells in our body experience stress & pressure via oxidative stress. As a result of this cellular stress, reactive oxidative species(ROS) are produced by auto reactive T-cells. Our body is capable of producing & utilizing antioxidants that can help neutralize these oxidative free radicals. However when a cell's oxidative capacity is deficient or the body is lacking antioxidants, production of free radicals ramps up out of proportion which can cause havoc on cells & create pro-inflammatory conditions. These proinflammatory conditions triggered by T-cells directly impact hair follicles, thereby leading to development of Alopecia Areata.

A recent meta analysis of 18 studies published in 2020 found that current evidence suggests Alopecia Areata is associated with oxidative stress, but further studies are required to further ratify this association.

Biomarkers associated with oxidative stress that triggers development of Alopecia Areata are high in case of severe form of this disease.

Superoxide dismutase(SOD) is a major antioxidant enzyme used to protect against the damage caused by superoxide anion. Dysfunction in Superoxide dismutase(SOD) was associated with the development of Alopecia Areata[30]. Superoxide dismutase(SOD) also becomes antigenic when continuously exposed to nitrogen & reactive oxidative species(ROS)[31]. Abdel Fattah et al found that the decreased level of Superoxide dismutase(SOD) was inversely correlated with severity of Alopecia Areata. Higher the severity of Alopecia Areata, the lower the level of Superoxide dismutase(SOD)[32]. Rasheed et al. found that nitric oxide-damaged erythrocyte Superoxide dismutase(SOD) triggers auto antibodies in case of Alopecia Areata.

In presence of Glutathione, Glutathione peroxidase (GSH-Px) converts H_2O_2 into water & oxygen[34] & neutralizes a number of peroxides. Naziroglu et al discovered that plasma & erythrocyte GSH-Px was found to be at lower level in case of patients suffering from Alopecia Areata[35].

Paraoxonase 1 (PON 1) is associated with HDL & contributes to antiatherogenic effects of HDL[36]. Lower activity of this enzyme has been found in tissues of patients suffering from Alopecia Areata.

Glutathione is a powerful antioxidant with power to neutralize reactive oxidative species(ROS) & also act as cofactor for antioxidant enzymes. A majority of Glutathione rich foods are metabolized by gut microbes. It was found that patients suffering from Alopecia Areata had low plasma and erythrocytes levels of Glutathione[37]. This indicates the role of gut microbiota in pathogenesis of Alopecia Areata.

Some of the essential fat soluble vitamins such as Beta Carotene & Vitamin E protects cell membranes against lipid peroxidation[39].Naziroglu et al. found that patients suffer from Alopecia Areata had significant low levels of beta-carotene in plasma and erythrocytes[39].

One of the richest sources of antioxidants, polyphenols including Resveratrol, Flavonoids, Phenolics, Anthocyanins, EGCG & more are beneficial for host metabolic,digestion & immune system health. It has been found that only 5%-10% of antioxidants are absorbed in the small intestine, mainly those with monomeric, and dimeric structures[40]. Balance 90%-95% are metabolized by gut microbiota & synthesize them into beneficial secondary metabolites. These metabolites play an important role in the prevention of Alopecia.

In one of the ex-vivo studies involving hair follicle cultures, polyphenols were found to enhance the proliferation of human dermal papilla cells by 30.3%. They were also shown to extend the human hair shaft by 30.8% when compared with controls[41].

In a clinical research, taking seaweed as a supplement was found to promote scalp growth & stop patterned hair loss[42].

With studies supporting association between Oxidative Stress & Alopecia Areata & role of gut microbiome in neutralizing Oxidative stress via conversion of non-enzymatic antioxidants into beneficial compounds, gut microbiota has a role to play in pathogenesis of Alopecia Areata. Major source of non- enzymatic antioxidants are polyphenol compounds in various foods.

Numerous studies analyzed the role of gut microbiota in onset & progression of Alopecia Areata. List of studies are enumerated in table 2[43].

Role of Fecal Microbiota Transplant(FMT) in Alopecia Areata

Fecal Microbiota Transplant(FMT) has been used as a therapy to overcome a number of life threatening conditions such as Clostridium Difficile Infection[56]. Fecal Microbiota Transplant is the administration & transfer of fecal matter from a healthy donor into the intestinal tract of recipient(patient) in order to alter & restore gut microbiota composition for the purpose of improving health & bringing the body back in the state of balance[57][58]. Recently the Food & Drug Administration(FDA) approved Fecal transplant therapy for recurrent Clostridium Difficile infection[59].

There are indications that Fecal Microbiota Transplant have therapeutic potential to treat a number of chronic diseases & conditions such as Irritable Bowel Syndrome, Obesity, Metabolic Syndrome & autoimmune diseases such as Alopecia[56].

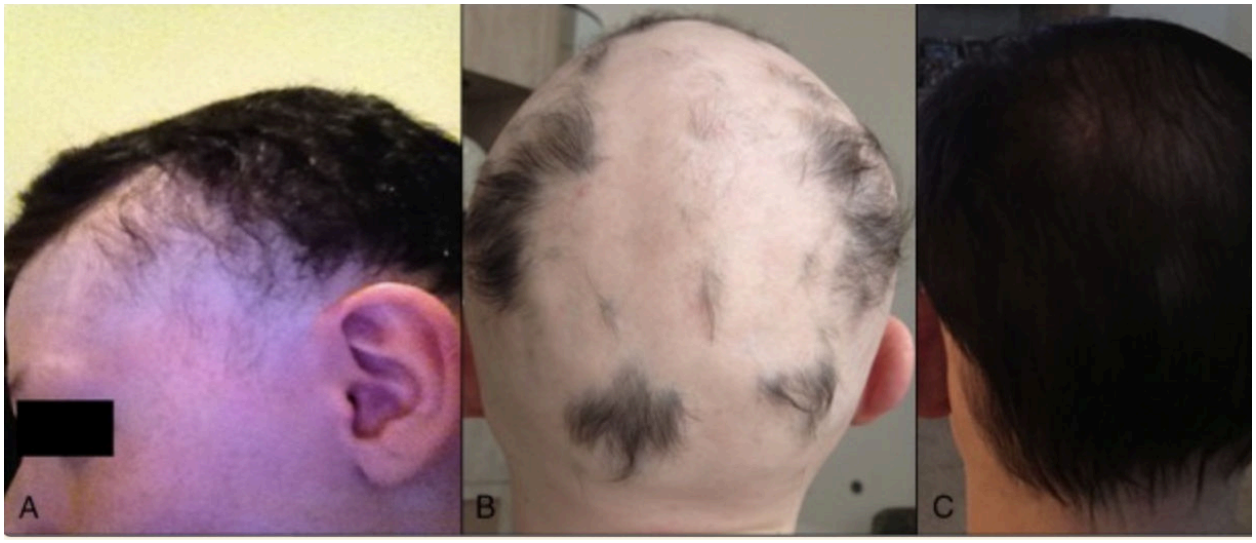
If we go back 5 decades, Eiseman & team of colleagues explained the use of fecal enemas to treat pseudomembranous colitis, thereby paving the way for Fecal Transplant as effective therapy in modern mainstream medicine[60].

The process of Fecal Microbiota Transplant(FMT) involves selecting a donor with no family history of autoimmune disease, metabolic syndrome & more & evaluating for potential pathogens. The feces are then prepared by mixing with water or normal saline & then filtered to remove any particulate matter.The mixture can be transported through different ways a nasogastric tube, nasojejunal tube, esophagogastroduodenoscopy, colonoscopy, or retention enema[61].

In a study published in 2017, two Alopecia patients recovered from Alopecia & their hair after undergoing Fecal Microbiota Transplant(FMT) therapy[62].

Case 1: A 20 year old man suffering from inflammatory Crohn’s disease, after going through 5 recurrent cycles of antibiotics, was treated under Fecal Microbiota Transplant(FMT). Two years prior to going for Fecal Microbiota Transplant(FMT), he was suffering from Alopecia Universalis which was being managed through steroids, immunosuppressants & laser treatments with no measurable outcomes. Upon treatment by Fecal Microbiota Transplant(FMT), he experienced significant improvement in his hair loss. After FMT therapy, his hair was grown in other areas as well. The following figure showcases improvement in hair loss by 2 grades[62].

Fig4[62]

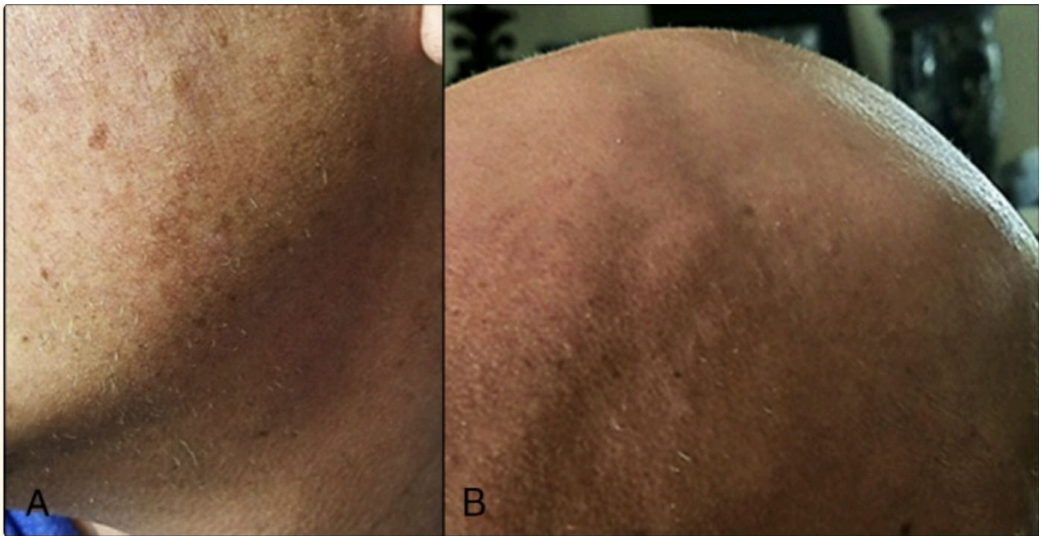


A-When patient started losing hair at age of 16
B-Patient's scalp after few months
C-Hair growth after Fecal Microbiota Transplant(FMT) therapy

This form of Alopecia Universalis treatment using Fecal Microbiota Transplant(FMT) therapy suggests a strong immune response to FMT.

Case 2: A 38 year old man suffering from Alopecia Universalis was diagnosed with blood diarrhea 10 years before & abdominal pain. Further investigation depicted the patient was suffering from inflammation of terminal ileum. Cycles of metronidazole improved Clostridium Difficile infection. Upon Fecal Microbiota Transplant(FMT) therapy treatment, the patient found sustainable resolution for Clostridium Difficile Infection(CDI). In follow up after FMT therapy, his hair was grown on head, face & arm[62].

Fig 5[62]



A: Growth of hair on head 8 weeks after FMT Therapy
B: Growth of hair on face 8 weeks after FMT Therapy

These case studies depict the successful role of Fecal Microbiota Transplant(FMT) therapy in treating Alopecia versus treating hair loss using immunosuppressants, antibiotics & more.

Conclusion

Alopecia is an autoimmune disease caused by pro-inflammatory metabolites released by gut microbes when the gut becomes permeable & triggers Leaky Gut syndrome. Besides gut dysbiosis & leaky gut, there are other multiple factors that are connected with pathogenesis of Alopecia. Although, there are not much evidence on direct association between gut dysbiosis & development of Alopecia, correlation between gut dysbiosis & other autoimmune diseases such as Arthritis, Hashimotos & more & association between Alopecia & other autoimmune diseases, rebalancing gut microbiota using Fecal Microbiota Transplant(FMT) therapy offers huge therapeutic potential to cure various forms of Alopecia. There is a need to conduct further studies with a bigger & diverse sample size to elucidate this inflammation-Alopecia connection. This would provide more relevant insights & relevant molecular signatures on how regulating activities of gut microbiota not only through FMT, but also through precision nutrition to transit from just managing Alopecia to actually prevent & reverse this autoimmune disease.

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41 Enhancement of Human Hair Growth Using Ecklonia cava Polyphenols
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42 Efficacy of Cistanche Tubulosa and Laminaria Japonica Extracts (MK-R7) Supplement in Preventing Patterned Hair Loss and Promoting Scalp Health
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The gut microbiome and Alopecia areata: Implications for early diagnostic biomarkers and novel therapies
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