THYROID HORMONE AND INTESTINAL MICROBIOME

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INTRODUCTION

Microbiota composition is one of the key components involved in the processes of the human body, particularly within the immune response. To maintain homeostasis within the body, a very strong collaboration between immune responses coupled with intestinal microbiota is essential. The pleiotropic effect exerted by the intestinal microbiota has been noticed as it has several effects on immune system development and the metabolism of nutrients. Metabolic products produced by microbiota serve as a cross-link between immune and epithelial cells and have the potential to damage the immune system. This also encompasses self-tolerance and auto-aggressive damage. The level of thyroid hormones in the body is influenced by the microbiota by controlling various functions like iodine uptake, degradation, and enterohepatic cycling. Interaction between host and microbiota has a significant effect on the minerals associated. The microbiota helps the host to develop immunity and the host regulates the microbiota through the defense mechanisms of the intestinal barrier. The barrier that separates microbiota and host contains various chemical, epithelial, and immunological components. This article is aimed at analyzing the interaction and effects of microbiota in thyroid hormones and how they impact the human body.

Thyroid synthesis and regulation

Thyroid hormones are produced by the thyroid gland, a small gland that is located below Adam's apple in the neck. Thyroid hormones play a significant role in bodily functions like heart rate, skin maintenance, digestion, and the rate at which calories are burned, etc. T4: Thyroxine and T3: Triiodothyronine is the two thyroid hormones.

The thyroid gland utilizes the iodine in the body and processes it into thyroid hormones. When the thyroid hormones are used, some of the iodine present in the hormone is released and returned to the thyroid gland. This is then used again to produce more thyroid hormones. Decreased iodine intake can cause iodine deficiency and low thyroid hormone synthesis. For maintaining proper feedback mechanism and homeostasis the Thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland, the Thyrotropin-releasing hormone (TRH) secreted from the hypothalamus, and T4 plays a significant role.

The thyrocytes present in the thyroid follicles produce Thyroglobulin (Tg), a precursor protein that does not contain iodine. The phosphorylation of Protein Kinase causes increased activity of Na + I - symporter to bring iodide from the circulation to the thyrocytes and the enzyme thyroid peroxidase oxidizes iodide into Iodine. Then the tyrosine residues of thyroglobulin combine with iodine to produce Monoiodothyrosine (MIT) and Diiodothyrosine (DIT). These iodinated residues combine to make T3 and T4. A negative feedback control mechanism regulates the amount of circulating thyroid hormone. When the levels are too high they suppress the production of TSH and TRH thus inhibiting their production.

Intestinal microbiota

It has been analyzed that the human microbiota comprises about 39 trillion bacteria, in a 70 kg person. The microbiota has gained significance because 20% of blood metabolites are derived from commensal bacteria. The human microbiota comprises many fungal, bacterial, archaeal, and viral taxa. In the human body, the intestine is the main location of the human microbiota. It is reported that the intestinal microbiota has around a hundred times as many genes as there are in the human genome.

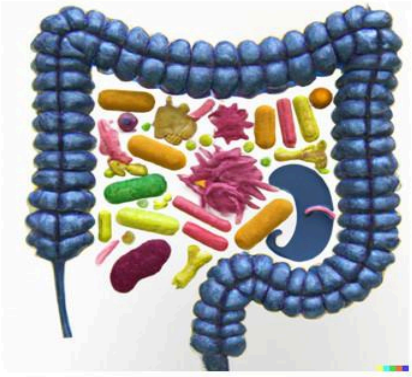

Fig 1: Gut microbiota

The relationship between intestinal microbiota and humans is mutualistic. The intestinal microbiota has broad impacts on maintaining the intestinal epithelium, resistance to pathogens, controlling immune function, metabolizing dietary and pharmaceutical compounds, and even behavior through the gut-brain axis. Some human intestinal microorganisms help the host by fermenting nutritional fibers into short-chain fatty acids (SCFA), such as acetic acid and butyric acid, which are then absorbed by the host. Intestinal bacteria play a role in metabolizing bile acids. The importance of SCFAs and other compounds they produce are similar to hormones and the intestinal microbiota itself appears to function as an endocrine organ. The dysregulation of the intestinal microbiota has been correlated with a host of inflammatory and autoimmune conditions.

Intestinal microbiota and autoimmune thyroid diseases (AITDs)

The endocrine system is greatly influenced by bacteria using various mechanisms like the metabolism of bile-excreted hormones, and conversion of various exogenous molecules to endocrine active derivatives. The production of short-chain fatty acids and lipopolysaccharides is also a part of the mechanism done by the endocrine system. Almost 2 to 5 percent of the population is affected by autoimmune thyroid disease. Several hypothesized mechanisms like the generation of self-antigens, lipopolysaccharide-induced toll-like receptor activation, induction of Type 1 to Type 2 T helper cell shift, etc suggest that the diversities in the microbiota contribute to the development of AIDS.

The major cause of hyperthyroidism is Grave's disease and Hashimoto's thyroiditis is considered the major cause of hypothyroidism.

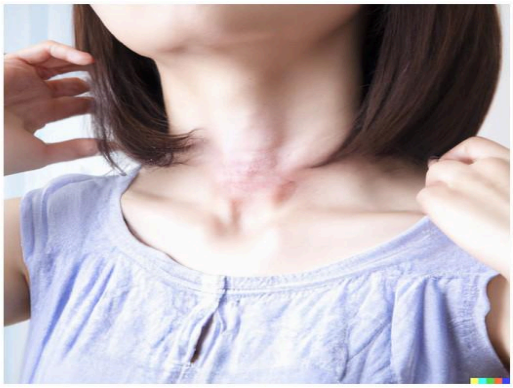

Fig 2: Patient with AITD

Graves disease(GD) is considered the major contributing factor to the development of hyperthyroidism. The circulating antibodies against the TSH receptor are the main immunologic

feature of Graves disease. The susceptibility genes of GD include two thyroid-specific genes, thyroglobulin and TSH receptor ones, and the genes involved in the immune regulation as CD40, FOXP3, HLA, PTPN22, FCRL3, CTLA-4, and CD25. The altered equilibrium loss between the pro-and anti-inflammatory cytokine milieu induces the synthesis of B-lymphocytes of anti-thyrotropin receptor antibodies (TRAb) which binds to the TSH receptor for mimicking TSH action.

The intestine of patients suffering from GD contains a higher level of antibodies against Helicobacter pylori and Yersinia enterocolitica, less colonization by Bacteroides, and greater colonization by yeast, compared to the healthy intestine. From various studies, it is analyzed that patients with Grave's disease synthesize antibodies like anti-transglutaminase, anti-yeast, and anti-gliadin. The studies in hyperthyroid patients found a higher abundance of Prevotellaceae, Pasteurellaceae, and Enterococcus spp. and a significant reduction in Enterobacteriaceae, Veillonellaceae, Rikenellaceae, Bifidobacteria, and Lactobacillaceae.

Hashimoto Thyroiditis (HT) is the major cause of hypothyroidism which is most common among autoimmune diseases. The main feature of Hashimoto's Thyroiditis is the presence of antibodies and autoreactive T cells against thyroperoxidase and thyroglobulin which causes the destruction of the thyroid gland.

From various studies, it is analyzed that the transfer of microbiota from conventional to specific pathogen-free (SPF) rats increased their susceptibility to Hashimoto Thyroiditis because of Lactobacillus spp. and Bifidobacterium spp. induce antibodies that cross-react with the enzyme thyroperoxidase and thyroglobulin

Intestinal microbiota and mineral uptake

Thyroid dysfunction occurs when minerals that support thyroid levels like selenium, iron, and zinc show abnormal levels.

Looking into each mineral we analyze the following. Many proteins that are involved in thyroid metabolism consist of Selenium. Examples of such proteins involve thioredoxin reductase, glutathione peroxidase, and type I II and III iodothyronine deiodinases (D1, D2, and D3).
The microbes compete with the host to metabolize the selenium. It was analyzed that selenium contributes to the increased microbial diversity in mice, with an increase in Bacteroidetes and a decrease in Parabacteroidetes. It is assumed that selenium is positively contributing to the relative abundance of Bifidobacterium adolescentis in the intestine and promotes the growth of this genus

Iron (Fe) is present in the active center of the enzyme Thyroperoxidase. It is absorbed as Fe (II) in the duodenum where the pH is approximately 6. The reduction of pH by secreting SCFAs can increase the absorption of iron by the host, orchestrated by the microbiota. It was analyzed that the supplementation of iron in humans causes an increase in the Enterobacteriaceae and Bacteroidetes members and a decrease in Lactobacillaceae and Bifidobacteria groups.

In humans, Zinc (Zn) deficiency causes a decreased level of TSH, T4, and T3 serum levels. The activity of the enzyme D2 that converts T4 to active T3 is enhanced by Zn. The relationship between Zn and thyroid metabolism is inversely related because hypothyroidism can induce Zn deficiency and Zn deficiency can contribute to the cause of hypothyroidism.

From these studies, it was analyzed that the Lactobacillaceae and Bifidobacterium spp. have a negative correlation with dietary iron and are positively related to Zn and Se. So we can say that

the regulation of these mineral levels may contribute to Hashimoto's Thyroiditis and Grave's Disease.

Influence of microbiota on the hypothalamus-pituitary axis

The intestinal microorganisms can synthesize different neurotransmitters such as dopamine, serotonin, noradrenaline, etc. The neurotransmitter dopamine can inhibit the secretion of TSH by inhibiting the activity of the anterior pituitary gland which may influence thyroid function. Thus it is analyzed that the microbiota can regulate the hypothalamus-pituitary axis. The studies in germ-free rats reported 25% higher TSH levels than controls

The cytokines induced by the Gram-negative bacterial LPS influence the pathogenesis by inhibiting hepatic type I iodothyronine deiodinase (D1) which helps to convert T4 to T3 and induces the type II iodothyronine deiodinase (D2). This can lead to the suppression of TRH and TSH release in the central nervous system.

Influence of bile acids in hypothyroidism

The microbiota like Bacteroides, Eubacterium, Peptostreptococcus, Bifidobacterium, Rumicoccus, Propionibacterium, Clostridium, Streptococcus, Lactobacillus, Escherichia, Methanobrevibacter can synthesize secondary bile acids from bile salts and it is assumed that clostridia are the most active from the above. The secondary bile acids are absorbed passively from the colon which causes systemic effects. They can influence the TSH level and can regulate energy metabolism. Studies in patients with subclinical hypothyroidism reported a decreased total bile acid level in the blood.

It is analyzed that the secondary bile acid- deoxycholic acid was dominant in hypothyroidism and chenodeoxycholic acid was dominant in hyperthyroidism. The small intestinal bacterial overgrowth which is common in patients with hypothyroidism leads to higher levels of secondary bile acids.

Conclusion

Human health and disease are strongly associated with intestinal microbiota. According to reports, it has been identified that the altered intestinal microbiota composition contributes to Hashimoto's thyroiditis and Grave's disease. The minerals like selenium, iron, and zinc have a vital role in the interaction between the intestinal microbiota and the host. It is also reported that the intestinal microbiota favors the development of AutoImmune Thyroid Diseases(AITDs) through various mechanisms. The studies suggest that Lactobacillaceae and Bifidobacteria spp have positive effects on AITD.

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