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Zoology

Thyroid Health & Methylation: What is the Link?

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Abstract **Review Article**

Thyroid is a ductless alveolar gland found in the neck just below the laryngeal prominence commonly known as Adam's apple. Thyroid function is controlled by the pituitary gland located in the brain. The pituitary produces thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to release thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4). The thyroid hormones play multifaceted roles in organ development and in the homeostatic control of fundamental physiological mechanisms such as body growth and energy expenditure in all vertebrates. In this article, we discuss the anatomy, cellular structure, embryology, endocrine physiology and clinical relevance of the thyroid gland as well as explore the link between thyroid health & methylation.

Keywords: Goiter, Methylation, Thyroxine (T_3), Triiodothyronine (T_4), Thyroid Stimulating Hormone (TSH).

INTRODUCTION

The thyroid gland is an endocrine organ located in the anterior part of the lower neck, just below the larynx. It is made up of two lobes joined by a small bridge of thyroid tissue called the *isthmus*. The gland is usually larger in women than in men and increases in size during pregnancy. The main function of the thyroid gland is to make hormones, thyroxine (T_4) and triiodothyronine (T_3), which are essential for the regulation of metabolic processes throughout the body. On a worldwide scale, approximately 200 million people have some form of thyroid disease. People of all ages and races can get thyroid disease. However, women are 5 to 8 times more likely than men to get problems with their thyroid function [1].

Anatomy

The thyroid gland is a butterfly-shaped organ composed of two elongated lateral lobes connected in the midline by a narrow tissue band called the *isthmus*. It is a brownish-red gland located anteriorly in the lower neck, extending from the level of the fifth cervical (C_5) vertebra down to the first thoracic (T_1) vertebrae. The gland varies from an H to a U shape and weighs nearly 10-15 grams in normal adults, with each lobe measuring about 5 cm long, 3 cm wide, and 2 cm thick. The isthmus measures about 1.25 cm in height and width. Typically, four parathyroid glands, two on each side, lie on each side between the two layers of the thyroid capsule, at the back of the thyroid lobes [2].

The thyroid is a highly vascular structure that receives its blood supply from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk. The superior thyroid artery supplies the upper half of the thyroid in over 95% of people. The lower portion of the thyroid is commonly supplied by the inferior thyroid artery, which may be absent or duplicated in a subset of the population. The venous blood is drained via superior and middle thyroid veins, which drain to the internal jugular vein, and via the inferior thyroid veins. In addition, the thyroid has extensive lymphatic drainage involving multiple levels of lymph nodes, including but not limited to the prelaryngeal (or Delphian), pre- and paratracheal, retropharyngeal, retroesophageal, and internal jugular lymph nodes [3].

Microanatomy

At the microscopic level, thyroid gland comprises of three primary features - *thyroid follicles*, *thyroid follicular cells*, and *parafollicular cells*. The lobes of the gland, as well as the isthmus, contain many small globular sacs called follicles [4]. The follicles are lined with follicular cells and are filled with a fluid known as *colloid* that contains the prohormone thyroglobulin. The follicular cells contain the enzymes needed to synthesize thyroglobulin, as well as the enzymes needed to release thyroid hormone from

thyroglobulin. When thyroid hormones are needed, thyroglobulin is reabsorbed from the colloid in the follicular lumen into the cells, where it is split into its component parts, including the two thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). The hormones are then released, passing from the cells into the circulation. Another type of cells known as parafollicular cells are scattered among follicular cells and in spaces between the spherical follicles. Parafollicular cells are also known as C cells as they secrete calcitonin hormone, which helps regulate calcium and phosphate levels in the blood [5].

Anatomical Variations

The thyroid gland may show several variations that can affect the way thyroid operates and thus result in various disorders. In a study of 52 male cadavers and 18 females, 9.6% of the males and 5.6% of females were missing the isthmus in their thyroid gland [6]. In some cases, the lobes of the thyroid may be of different sizes from one another. Some individuals have a pyramidal lobe, which is considered a third lobe in the thyroid that stems out from the isthmus. Some thyroid glands may or may not have levator glandulae thyroideae, a fibrous band that stretches from a pyramidal lobe to the isthmus. In certain cases, the thyroid gland can become enlarged (goiter) or develop clumps of cells called as thyroid nodules, which are often benign but can sometimes indicate thyroid cancer.

Embryology

The thyroid gland is the first endocrine organ to form during fetal development. At 3-4 weeks of gestational age, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the primitive tongue. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through a narrow canal, the *thyroglossal duct*. Over the next few weeks, it migrates to the base of the neck, passing in front of the hyoid bone. During migration, the thyroid remains connected to the tongue by the thyroglossal duct. At the end of the fifth week the thyroglossal duct degenerates, and over the following two weeks the detached thyroid migrates to its final position. The thyroid gland reaches its final shape and relative size by seven weeks gestation [7]. In normal development, the connection between the thyroid and the thyroglossal duct regresses around five weeks of gestational age. However, if this regression does not occur, a thyroglossal duct cyst may form. The most common congenital anomaly of the thyroid, thyroglossal duct cysts are seen in 7% of adults, appearing as 2-3 cm fusiform or spherical nodules in the midline neck, which move upon swallowing.

Function

The thyroid gland is a vital part of the human endocrine system. It plays a key role in the metabolism, growth, and development of the human body. The primary function of the thyroid gland is the production of the iodine- containing thyroid hormones, *thyroxine* (T_4) and *triiodothyronine* (T_3) and the peptide hormone *calcitonin*. The thyroid hormones are created from iodine and tyrosine. T_4 is so named because it contains four atoms of iodine per molecule while T_3 contains three atoms of iodine per molecule [8]. The thyroid hormones regulate many vital body functions such as breathing, heart rate, central and peripheral nervous system function, metabolism, body weight, digestion, muscle strength, bone growth, brain development, menstrual cycles, body temperature, cholesterol levels and so forth.

Thyroid Hormones

Thyroid-stimulating hormone, also known as TSH, is a glycoprotein hormone produced by the anterior pituitary. It is the primary stimulus for thyroid hormone production by the thyroid gland. It also exerts growth effects on thyroid follicular cells leading to enlargement of the thyroid. The hypothalamic-pituitary axis regulates TSH release. Specifically, neurons in the hypothalamus release *thyroid-releasing hormone* or TRH, which stimulates thyrotrophs of the anterior pituitary to secrete TSH. TSH, in turn, stimulates thyroid follicular cells to release thyroid hormones in the form of T_3 or T_4. *Triiodothyronine*, or T3, is the active form of thyroid hormone. Though it represents only 20% of the released hormone, the majority of T_3 comes from the peripheral conversion of T_4 to T_3. *Tetraiodothyronine*, also known as thyroxine or T_4, constitutes more than 80% of the secreted hormone. Thyroxine is a relatively inactive prohormone. When released into the circulation, it forms T3 through the process of de-iodination. T_4 and T_3 can then exert negative feedback on the anterior pituitary with high levels of T_3/T_4 decreasing TSH secretion and low levels of T3/T4 increasing TSH release [9].

One of the most important elements behind producing thyroid hormones is *iodine*, which we get a majority of through food or supplements. Both T_3 and T_4 need iodine in order to be produced by the thyroid gland. Once iodine makes its way to the thyroid it gets converted into T_3 and T_4. These are then released into the bloodstream to help with multiple functions like increasing the metabolic rate in the body, growth, brain development, and so forth. Some of the highest dietary sources of iodine include cheese, cow's milk, eggs, saltwater fish, soy milk, and yogurt. In addition, there are other hormone-producing cells within the thyroid gland called C-cells. These cells produce a hormone known as *calcitonin*. Calcitonin plays a significant role in regulating calcium and phosphate levels in the blood, which is important for your bone health and maintenance [10].

Biochemistry of Thyroid Hormones

Thyroxine (T_4) and triiodothyronine (T_3) contain iodine and are formed from thyronines, which are composed of two molecules of the amino acid tyrosine. Thyroxine contains four iodine atoms, and triiodothyronine contains three iodine atoms. Since each molecule of tyrosine binds one or two iodine atoms, two tyrosines are used to synthesize both thyroxine (T4) and triiodothyronine (T_3). These two hormones are the only biologically active substances that contain iodine, and they cannot be produced in the absence of iodine. The process leading to the eventual synthesis of thyroxine and triiodothyronine begins in the thyroid follicular cells, which concentrate iodine from the serum. The iodine is then oxidized and attached to tyrosine residues to form compounds called iodotyrosines within thyroglobulin molecules [11]. The iodinated tyrosine residues are then rearranged to form thyroxine and triiodothyronine. Therefore, thyroglobulin serves not only as the structure within which thyroxine and triiodothyronine are synthesized but also as the storage form of the two hormones.

Synthesis of Thyroid Hormones

The thyroid hormones are created from thyroglobulin. It is a protein within the colloid in the follicular lumen that is originally created within the rough endoplasmic reticulum of follicular cells and then transported into the follicular lumen. Thyroglobulin contains 123 units of tyrosine, which reacts with iodine within the follicular lumen.

Iodine is essential for the synthesis of the thyroid hormones. Iodine (I^0) travels in the blood as iodide (I^-), which is taken up into the follicular cells by a sodium-iodide symporter. This is an ion channel on the cell membrane which in the same action transports two sodium ions and an iodide ion into the cell. Iodide then travels from within the cell into the lumen, through the action of pendrin, an iodide-chloride antiporter. In the follicular lumen, the iodide is then oxidized to iodine. This makes it more reactive, and the iodine is attached to the active tyrosine units in thyroglobulin by the enzyme thyroid peroxidase. This forms the precursors of thyroid hormones monoiodotyrosine (MIT), and diiodotyrosine (DIT) [12].

When the follicular cells are stimulated by thyroid-stimulating hormone (TSH), the follicular cells reabsorb thyroglobulin from the follicular lumen. The iodinated tyrosines are cleaved, forming the thyroid hormones T_4, T_3, DIT, MIT, and traces of reverse triiodothyronine. T_3 and T_4 are released into the blood. The hormones secreted from the gland are about 80–90% T_4 and about 10–20% T_3. Deiodinase enzymes in peripheral tissues remove the iodine from MIT and DIT and convert T_4 to T_3 and RT_3. This is a major source of both RT_3 (95%) and T_3 (87%) in peripheral tissues [13].

Regulation of Thyroid Hormones

The hypothalamus-pituitary-thyroid (HPT) axis determines the set point of thyroid hormone (TH) production. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the synthesis and secretion of pituitary thyrotropin (thyroid-stimulating hormone, TSH), which acts at the thyroid to stimulate all steps of TH biosynthesis and secretion. The Hypothalamus detects a low plasma concentration of thyroid hormone and releases *Thyrotropin-Releasing Hormone* (TRH) into the hypophyseal portal system. TRH binds to receptors found on thyrotrophic cells of the anterior pituitary gland, causing them to release *Thyroid Stimulating Hormone* (TSH) into the systemic circulation [14]. TSH binds to TSH receptors on the basolateral membrane of thyroid follicular cells and induces the synthesis and release of thyroid hormone. The THs thyroxine (T4) and triiodothyronine (T3) control the secretion of TRH and TSH by negative feedback to maintain physiological levels of the main hormones of the HPT axis [15]. Reduction of circulating TH levels due to primary thyroid failure results in increased TRH and TSH production, whereas the opposite occurs when circulating THs are in excess.

Clinical Relevance

Thyroid diseases are very common and can affect anyone whether men, women, infants, teenagers and the elderly. It can be present at birth or can develop as a person age. An estimated 20 million people in the Unites States have some type of thyroid disorder. A woman is about five to eight times more likely to be diagnosed with a thyroid condition than a man [16]. Thyroid diseases can range from a small, harmless goiter (enlarged thyroid gland) that needs no treatment to life-threatening cancer.

Functional Disorders

The most common thyroid disorders involve abnormal production of thyroid hormones. Too much production of the thyroid hormone results in a condition known as *hyperthyroidism* while insufficient thyroid hormone production leads to *hypothyroidism*. Most thyroid disorders can be managed well if diagnosed and treated properly [17]. Some individuals may be at a higher risk of developing a thyroid disease if they:

1. Have a family history of thyroid diseases.
2. Take a medication that's high in iodine (amiodarone).
3. Are older than 60, especially in women.
4. Have had treatment for a past thyroid condition or cancer (thyroidectomy or radiation).
5. Have had a thyroid problem before, such as a goiter.
6. Have been pregnant or delivered a baby within the past 6 months.
7. Have Turner syndrome, a genetic disorder that affects females.
8. Have other autoimmune diseases, including.

a. Sjogren's syndrome, characterized by dry eyes and mouth.
b. Pernicious anemia, a vitamin B12 deficiency.
c. Type 1 diabetes [31, 35].
d. Rheumatoid arthritis.
e. Lupus, a chronic inflammatory condition.

People should get tested regularly to help uncover thyroid problems especially subclinical problems, where a person has no apparent symptoms.

Hypothyroidism

An underactive thyroid gland results in hypothyroidism. Hypothyroidism is a disorder that occurs when the thyroid gland does not produce enough thyroid hormone to meet the body's needs. Thyroid hormone regulates metabolism and affects nearly every organ in the body. Without enough thyroid hormone, many of the body's functions slow down.

Hypothyroidism is one of the most common thyroid disorders and affects people all over the world irrespective of age, sex, and race. Women are much more likely than men to develop hypothyroidism. About 4.6 percent of the U.S. population age 12 and older has hypothyroidism. However, it is more common among people older than sixty years. Iodine deficiency is the most common cause of hypothyroidism worldwide and the autoimmune disease Hashimoto's thyroiditis is the most common cause in the developed world [18, 32].

Causes

Hypothyroidism has several causes, including:

1. **Hashimoto's Disease:** It is an autoimmune disorder in which the immune system attacks the thyroid, causing inflammation and interfering with its ability to produce thyroid hormones. Hashimoto's disease is also known as chronic lymphocytic thyroiditis. It is the most common cause of hypothyroidism in the United States [19].
2. **Thyroiditis:** It is an inflammation of the thyroid that causes stored thyroid hormone to leak out of the thyroid gland. At first, the leakage raises hormone levels in the blood, leading to hyperthyroidism when thyroid hormone levels are too high that lasts for 1 to 2 months. Most people then develop hypothyroidism before the thyroid is completely healed.
3. **Congenital Hypothyroidism:** Refers to the hypothyroidism that is present at birth. Some babies are born with a thyroid that is not fully developed or does not function properly. If untreated, congenital hypothyroidism can lead to mental retardation and growth failure. Early treatment can prevent these complications, so most newborns in the United States are screened for hypothyroidism [20].
4. **Surgical Removal of the Thyroid:** When part of the thyroid is removed, the remaining part may produce normal amounts of thyroid hormone, but some people who have this surgery develop hypothyroidism. Removal of the entire thyroid always results in hypothyroidism. Part or all of the thyroid may be surgically removed as a treatment for:
   - Hyperthyroidism.
   - Thyroid cancer.
   - A large goiter, which is an enlarged thyroid that may cause the neck to appear swollen and can interfere with normal breathing and swallowing.
   - Thyroid nodules, which are noncancerous tumors, called adenomas, or lumps in the thyroid that can produce excess thyroid hormone.
5. **Radiation Treatment of the Thyroid:** Radioactive iodine, a common treatment for hyperthyroidism, gradually destroys the cells of the thyroid. Most people who receive radioactive iodine treatment eventually develop hypothyroidism. People with Hodgkin's disease, other lymphomas, and head or neck cancers are treated with radiation, which can also damage the thyroid.
6. **Medications:** Some drugs can interfere with thyroid hormone production and lead to hypothyroidism, including:
   - Amiodarone, a heart medication.
   - Interferon alpha, a cancer medication.
   - Lithium, a bipolar disorder medication.
   - Interleukin-2, a kidney cancer medication.

Postpartum thyroiditis occurs in 5% to 9% of women after childbirth and is usually a temporary condition. Some causes of hypothyroidism, such as postpartum thyroiditis and subacute thyroiditis may be transient and pass over time, and other causes such as iodine deficiency may be able to be rectified with dietary supplementation. Rarely, severe, untreated hypothyroidism may lead to *myxedema coma*, an extreme form of hypothyroidism in which the body's functions slow to the point that it becomes life threatening [21, 32, 34]. Myxedema requires immediate medical treatment.

Symptoms

Hypothyroidism has many symptoms that can vary from person to person. Some common symptoms of hypothyroidism are:

1. Fatigue.
2. Weight gain.
3. Puffy face.
4. Cold intolerance.
5. Joint and muscle pain.
6. Constipation.
7. Dry skin.
8. Dry, thinning hair.
9. Decreased sweating.

10. Heavy or irregular menstrual periods and impaired fertility.
11. Depression.
12. Slowed heart rate.

However, hypothyroidism develops slowly; so many people don't notice symptoms of the disease. Symptoms more specific to Hashimoto's disease are a goiter and a feeling of fullness in the throat [22, 35]. Hypothyroidism can contribute to high cholesterol, so people with high cholesterol should be tested for hypothyroidism.

Diagnosis

Several symptoms of hypothyroidism resemble those of other diseases therefore; hypothyroidism cannot be diagnosed based on symptoms alone. With suspected hypothyroidism, health care providers collect patient's medical history and perform a thorough physical examination. Several blood tests may be used to confirm a diagnosis of hypothyroidism and to find its cause:

1. **TSH Test:** The ultrasensitive TSH test is usually the first test a health care provider performs. This test detects even tiny amounts of TSH in the blood and is the most accurate measure of thyroid activity available [23, 31]. Generally, a TSH reading above normal means a person has hypothyroidism and a reading below normal means a person has hyperthyroidism. Mildly elevated TSH without symptoms indicates subclinical hypothyroidism. Some health care providers treat subclinical hypothyroidism immediately. Others prefer to leave it untreated but monitor their patients for signs that the condition is worsening. Health care providers may conduct additional tests to help confirm the diagnosis or determine the cause of hypothyroidism.
2. **T4 Test:** This test measures the actual amount of circulating thyroid hormone in the blood. In hypothyroidism, the level of T_4 in the blood is lower than normal.
3. **Thyroid Autoantibody Test:** This test looks for the presence of thyroid autoantibodies. Most people with Hashimoto's disease have these antibodies, but people whose hypothyroidism is caused by other conditions do not.

Treatment

Hypothyroidism cannot be cured but it can be treated and completely controlled in most people. Health care providers treat hypothyroidism with synthetic thyroxine, a medication that is identical to the hormone T_4. The exact dose depends on the patient's age and weight, the severity of the hypothyroidism, the presence of other health problems, and whether the person is taking other drugs that might interfere with how well the body uses thyroid hormone. Health care providers test TSH levels about 6 to 8 weeks after a patient begins taking thyroid hormone and make any necessary adjustments to the dose. Each time the dose is adjusted, the blood is tested again. Once a stable dose is reached, blood tests are normally repeated in 6 months and then once a year. Hypothyroidism can be completely controlled with synthetic thyroxine, as long as the recommended dose is taken every day as instructed by the doctor.

Hyperthyroidism

An overactive thyroid gland results in hyperthyroidism. Hyperthyroidism is a condition where the thyroid gland produces and secretes inappropriately high amounts of thyroid hormone which can lead to thyrotoxicosis. The prevalence of hyperthyroidism in the United States is 1.2% with overt hyperthyroidism accounting for 0.5% and subclinical hyperthyroidism accounting for 0.7%. It is most common in women between ages 20 and 40, but men can also develop this condition.

Causes

Hyperthyroidism has several causes, including:

1. **Graves' Disease:** is the most common cause of hyperthyroidism. It is an autoimmune disorder in which the immune system produces antibody proteins that stimulate the thyroid gland to make too much thyroid hormone [24]. It is chronic (long-term) and typically runs in families with a history of thyroid disease. A common characteristic of patients with Graves' disease is swelling behind the eyes that cause them to bulge outward.
2. **Thyroid Nodules:** It is commonly known as *Plummer's disease* and is more common in old people. Overactive thyroid nodules or lumps on the thyroid gland are common and usually not cancerous. However, one or more nodules may become overactive and secrete too much thyroid hormone.
3. **Thyroiditis:** Thyroiditis is inflammation of the thyroid gland. Some types of thyroiditis can cause thyroid hormone to leak out of the thyroid gland into the bloodstream [25]. As a result, a person may develop symptoms of hyperthyroidism. The types of thyroiditis that can cause hyperthyroidism include:
   - Subacute thyroiditis, which involves a painfully inflamed and enlarged thyroid.
   - Postpartum thyroiditis, which can develop after a woman gives birth.
   - Painless thyroiditis, which is similar to postpartum thyroiditis, but occurs in the absence of pregnancy.

Thyroiditis can also cause symptoms of hypothyroidism, or underactive thyroid. In some cases, after the thyroid gland is overactive for a period of time, it may become underactive.

- **Too much iodine:** The thyroid gland uses iodine to make thyroid hormone. The amount of iodine consumed affects thyroid hormone production by

the thyroid gland. In some people, consuming large amounts of iodine may cause the thyroid to make too much thyroid hormone. Some cough syrups and medicines may contain a lot of iodine. Seaweed and seaweed-based supplements also contain a lot of iodine.

- **Too much thyroid hormone medicine:** Some people who take thyroid hormone medicine for hypothyroidism may take too much. If a person takes thyroid hormone medicine, it is important to see the doctor at least once a year to have the thyroid hormone levels checked. There may be a need to adjust the dose if the doctor finds that the thyroid hormone level is too high. Some other medicines may also interact with thyroid hormone medicine and raise hormone levels. If a person takes thyroid hormone medicine, he or she may ask the doctor about interactions when starting new medicines.
- **Pituitary Adenoma:** is a noncancerous tumor of the pituitary gland that can cause hyperthyroidism by secreting excess TSH.

Untreated, hyperthyroidism can cause serious health problems, including:

a. An irregular heartbeat that can lead to blood clots, stroke, heart failure, and other heart-related problems.
b. An eye disease called Graves' ophthalmopathy [26].
c. Thinning of bones, osteoporosis, and muscle problems.
d. Menstrual cycle and fertility issues.

Symptoms

Symptoms of hyperthyroidism can vary from person to person and may include:

1. Anxiety, irritability and nervousness.
2. Trouble sleeping.
3. Losing weight.
4. An enlarged thyroid gland or a goiter.
5. Muscle weakness and tremors.
6. Irregular menstrual periods or no menstrual cycle.
7. Heat sensitivity.
8. Vision problems or eye irritation.
9. Rapid or irregular heartbeat.
10. Shaky hands, muscle weakness and tremors.
11. Frequent bowel movements.

In older adults, hyperthyroidism is sometimes mistaken for depression or dementia. Older adults may have different symptoms, such as loss of appetite or withdrawal from people, than younger adults with hyperthyroidism. Untreated, hyperthyroidism can cause serious health problems, including:

- An irregular heartbeat that can lead to blood clots, stroke, heart failure, and other heart-related problems.
- An eye disease called Graves' ophthalmopathy.
- Thinning bones, osteoporosis, and muscle problems.
- Menstrual cycle and fertility issues.

Diagnosis

A hyperthyroidism diagnosis can't be based on symptoms alone because many of its symptoms are the same as those of other diseases. The doctor may use several thyroid blood tests and imaging tests to confirm the diagnosis of hyperthyroidism and find its cause. Since hyperthyroidism can cause fertility problems, therefore women who have trouble getting pregnant often get tested for thyroid problems.

Treatment

Long-term management of hyperthyroidism may include drugs that suppress thyroid function such as propylthiouracil, carbimazole and methimazole. Alte rnatively, radioactive iodine-131 can be used to destroy thyroid tissue: radioactive iodine is selectively taken up by thyroid cells, which over time destroys them. The chosen first-line treatment will depend on the individual and on the country, where being treated. Surgery to remove the thyroid can sometimes be performed as a trans-oral thyroidectomy, a minimally invasive procedure. Surgery does however carry a risk of damage to the parathyroid glands and the recurrent laryngeal nerve, which innervates the vocal cords. If the entire thyroid gland is removed, hypothyroidism will inevitably result, and thyroid hormone substitutes will be needed.

Thyroid Health & Balanced Methylation

Methylation is a biochemical process that involves transfer of methyl groups back and forth from one substance to another. It is a complex process with numerous on/off switches involving the back and forth movement of methyl groups. Methylation (on) and de-methylation (off) happens thousands of times each second throughout our body. This mechanism is required for DNA production and repair, detoxification, histamine metabolism, estrogen metabolism, fat metabolism, cell energy, growth and development, cell differentiation, maintenance of cells, and many other things – including healthy thyroid function.

In the last several years, evidence points to dysregulation of methylation as one reason for autoimmune thyroid disorders like Grave's and Hashimoto's thyroid disease. Studies suggest that impaired methylation may cause some genes to inappropriately turn on, which can lead to increased risk of thyroid concerns. Dysfunctional methylation and inappropriate activity of genes sends inflammatory messages that causes immune cells to attack the thyroid and leads to autoimmune destruction.[27] Depending on which gene(s) are affected, it will trigger destruction

that leads to the disease presentation of Hashimoto's or Grave's disease.

MTHFR & Thyroid Dysfunction

MTHFR, or methyltetrahydrofolate reductase, is the name of both the gene and the enzyme that the gene produces. The enzyme is used to convert folic acid and folate into a form that the body can use, i.e. methylfolate, which is important for numerous biological processes. An individual's MTHFR composition is dependent upon the two genes from both parents. Depending on whether a person inherited zero, one or two MTHFR SNPs (pronounced snips), functioning may be reduced by as much as 30 to 70 percent.

The MTHFR enzyme is crucial for the body to methylate properly. When it does not, the risk for developing a number of diseases including autoimmunity and thyroid dysfunction rises [28]. When the MTHFR genes work properly, the body can more efficiently make proteins, use antioxidants, metabolize hormones, better eliminate toxins and heavy metals, and manage inflammation. All these functions are vital to managing Hashimoto's hypothyroidism. In certain cases of Hashimoto's hypothyroidism, the sufferer can develop a sluggish MTHFR enzyme. This happens because thyroxine (T_4) helps produce the body's most active form of vitamin B_2, flavin adenine dinucleotide (FAD). Vitamin B_2 must be converted into active FAD by T_4 so that the body can use it. The MTHFR enzyme must have enough FAD in order to do its job. If FAD levels are low due to too little T4, then the MTHFR enzyme slows down. This then leads to low methylfolate, and in turn, to low neurotransmitters and low SAMe (S-Adenosyl methionine).

Glutathione, methylation and folate are associated with MTHFR function and thyroid-related conditions. Glutathione is the most abundant detoxifier in the body. It keeps inflammation low, protecting you against disease. Having lower glutathione levels, people with MTHFR mutations are more vulnerable to stress, toxins, and illness. Research shows a direct correlation between a breakdown in the glutathione system and autoimmune disease, such as Hashimoto's disease. Autoimmune disease is linked to leaky gut, yet in order to have a healthy gut, maintenance of glutathione levels is necessary.

Methylation Concerns

The process of methylation depends on the availability of several nutrients. At the heart of this critical activity is folate along with vitamins B6, B12 and other B vitamins. Folic acid as methylated folate is the rate-limiting step of methylation. Folic acid (synthetic) must be converted to methylated folate in order to work. Unprocessed, non-fortified foods have natural (methylated) folate, whereas fortified foods have folic acid (unmethylated) added. Chicken and beef liver, cooked legumes/beans, asparagus, and spinach are some of the richest sources of natural folate.

It is estimated that at least 60 percent of the population or more has difficulty making enough methylated folate because how their methylation genes work. Some of the genes SNPs (single nucleotide polymorphisms) or mutations involved with methylation include MTHFR, MTR, MTRR, CBS, COMT, FUT_2, and TCN_2. Certain laboratory tests and ancestry-health genome tests may help to identify these genes. If one lacks adequate folate intake, it creates roadblocks for the methylation process.

Lack of nutrients in the diet is a significant concern for everyone. There are no perfect diets that supply all the necessary nutrients every day, especially with 21st Century challenges. Even when B vitamins are added to processed foods, methylation dysfunction can still occur. Foods with added synthetic (unmethylated) vitamin B_6 (pyridoxine HCl), B_{12} (cyanocobalamine), and folate as folic acid may create more stress for the methylation process. Humans have a reduced ability to convert folic acid to folate compared to animals. If it is not converted or used, it builds up in the body and is known as oxidized folic acid or "unmetabolized folic acid". This adversely affects several things, including methylation.

Unmetabolized Folic Acid Findings and Concerns

Methylation is a massive cellular process that requires folate and several other nutrients. It occurs trillions of times in every cell throughout the day. Build-up of unmetabolized folic acid adversely affects methylation. It is estimated that about 65 percent of the population has one MTHFR gene mutation and about 25 percent have two MTHFR gene mutations. When these genes are affected, the rate of methylation is lower, and this ultimately impairs folate metabolism. In order to bypass these MTHFR gene mutations, natural folate or methylated folate is preferred rather than folic acid. Further insight has occurred in recent years with the build-up of unmetabolized folic acid. Too much folic acid may interfere with the use of natural folate as it may affect its transportation and receptor sites in the intestinal tract and kidneys. Other concerns due to high levels of unmetabolized folic acid include impaired DNA synthesis, methylation and repair processes, along with increased incidence of colorectal cancer [29, 35, 32]. Too much unmetabolized synthetic folic acid can block how some medications work in the body. It is well known that taking folic acid or folate to the exclusion of other nutrients can mask or create other deficiencies. Taking folic acid without vitamin B_{12} may mask the deficiency of vitamin B_{12}, create anemia and affect cognitive function, especially in the elderly. Research also shows that the higher the level of unmetabolized folic acid in the blood stream, the more dysfunctional and compromised the natural killer cells became [33, 34].

Other Nutrients Needed for Methylation

In addition to the natural, coenzyme/methylated forms of folate, vitamins B_6 and B_{12}, other nutrients are needed for methylation. These include magnesium, calcium, zinc, selenium, molybdenum, methionine, and choline, etc. Trimethylglycine (TMG) which converts to S-adenosyl methionine or SAMe is another critical, make-or-break nutrient for methylation. TMG conversion into SAMe is also necessary for the amino acid tyrosine to convert into dopamine which helps supports healthy mood, energy, and focus. Mood distress, decreased energy, and diminished focus may be related with impaired thyroid function.

CONCLUSION

The thyroid gland and the hormones that it synthesizes are critically important to human development and a healthy life. The critical nature of thyroid function is reflected in the complex mechanisms that nature has established for the regulation of thyroid hormones. Because the thyroid system is so important to our everyday functioning, it's crucial to properly diagnose and treat any problems that occur. If a person has symptoms of either hypothyroidism or hyperthyroidism, it is important to check with the healthcare provider so as to get tested. Exercise (acute and long-term) supports methylation. In addition to the folate-rich foods, avocado, beets, broccoli, green leafy vegetables, brussels sprouts, legumes (peas, beans, lentils) and whole grain rice help support methylation. Choose organic foods when possible. Roundup/pesticide treated foods create more stress to the body and generally have fewer nutrients. Supplementation with coenzyme or methylated B vitamins may be quite helpful for many. In addition, magnesium and choline are frequently lacking in the diet and can also benefit methylation and thyroid health [30]. Taking thyroid hormone is one solution to thyroid problems. It, however, does nothing to address a fundamental physiological process integral to normal metabolism and thyroid function. Before the thyroid gets to the point of non- function because of autoimmune destruction and requires medical hormone replacement, we must provide our body with proper care. Quality foods and intentional nourishment is more critical today than ever before. Let us make it our resolution to intentionally nourish our body today to have a healthy tomorrow.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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