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A review on nanomedicines in treatment of thyroid and their applications in management of thyroid disorders

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***Abstract*---**Thyroid disease is a major issue all over the world. Thyroid illness is also very common in India. Numerous thyroid disease studies have revealed that 42 million Indians are affected by the disease. Thyroid ailments are classified into five types in India: hypothyroidism, hyperthyroidism, goitre and iodine deficiency disorders, Hashimoto's thyroiditis, and thyroid cancer. The epidemiology of these five diseases will be the subject of this review. Thyroid hormone replacement therapy has been used to treat hypothyroidism for over a century. For the majority of the twentieth century, the first pharmacological treatments were natural thyroid preparations (thyroid extract, desiccated thyroid, or thyroglobulin), which contained both thyroxine (T4) and triiodothyronine (T3) (T3). This article discusses briefly the current treatment options for common thyroid issues.

***Keywords*---**Hypothyroidism, Graves' disease, nanomedicine, thyroid cancer, Goiter.

1. Introduction

It is a disorder that affects the thyroid gland's ability to produce hormones, causing it to malfunction. An endocrine organ, the thyroid gland is positioned in

the front of the neck and generates thyroid hormones (1) that circulate in the bloodstream and influence several other organs' functions. To govern energy expenditure, baby growth, and childhood development, these hormones are generally found in the body's tissues. Symptoms vary depending on the type of thyroid disease. At the same time, a person can have a variety of sorts. In total, there are five categories:

1. Hypothyroidism (low function) is caused by a lack of free thyroid hormones in the body.
2. Too many unbound thyroid hormones create hyperthyroidism (high activity). The most prevalent structural abnormality is a goitre (enlargement of the thyroid gland)
4. Benign (not cancerous) or malignant tumours
5. Subclinical hypothyroidism or hyperthyroidism with abnormal thyroid function tests but no symptoms (2).

2. Anatomy and Normal Functions of the Thyroid Gland

The thyroid gland, shaped like a butterfly, is situated directly below the larynx, prior to the trachea. The left and right lobes form a wing-like structure on either side of the medial region, which is called the isthmus. The parathyroid glands are found on the posterior surfaces of the thyroid lobes. thyroid follicles constitute the majority of the gland's tissue. They are made up of an epithelial wall of cells surrounding an inner cavity filled with the sticky fluid known as colloid. It's here that thyroid hormone production takes place, and iodine, the vital and unique component, is crucial (3).

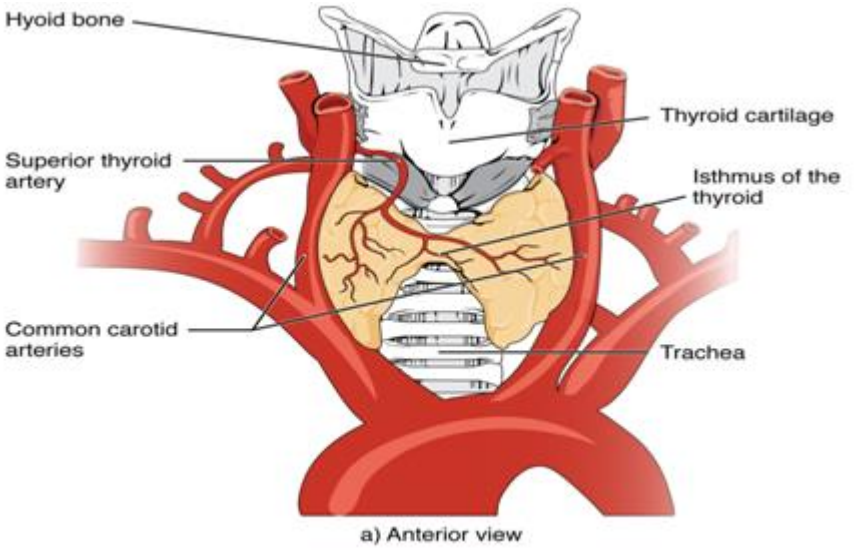

Fig 1 - Thyroid gland (Source – Google Images)

3. Synthesis and Release of Thyroid Hormones

The follicle cells secrete thyroglobulin, a glycoprotein that attaches to iodine atoms in the colloid to create hormones. The hormones are assembled in the following manner:
Sodium-Iodide Symporter-Mediated Active Transport of Iodide into Follicular Cells (NIS). A Sodium-Potassium ATPase maintains the sodium gradient driving this secondary active transport. There are two types of Thyroglobulin (Tg), both of which are big proteins with a high concentration of the amino acid Tyrosine.In the follicular lumen, Thyroglobulin is exocytosed into a colloidal form. Thyroid hormone is synthesised using thyroglobulin as a scaffold. The Thyroglobulin has been iodinated. Thyroid peroxidase, an enzyme, turns inactive iodide into a reactive compound. Monoiodotyrosine (MIT) and then diiodotyrosine (DIT) are formed when iodide attaches to the benzene ring of Tyrosine residues in Thyroglobulin (DIT). The Triiodothyronine (T3) and Tetraiodothyronine (T4) hormones are formed when MIT and DIT are coupled together. Thyroid hormone is extruded from cells and returned to them in this way: through endocytosis. The bigger protein thyroglobulin is broken down by proteolysis in lysosomes to release the iodine-containing tyrosine residues. The Thyroglobulin scaffold is subsequently recycled and free T3 or T4 is liberated.

The active thyroid hormones are T3 and T4. Thyronine Binding Globulin (TBG) and Albumin (Alcohol) are the two plasma proteins that primarily transport them. Because of its reduced affinity for the binding proteins, T3 is the more potent version, but it also has a shorter half-life. Unbound free T3 and T4 hormones make up less than 1% of total T3 and T4 hormones. T4 is deiodinated to T3, which is more active, in the periphery. Iodine is removed from T3 and T4 to deactivate them. There are two places where this occurs: the liver and the kidneys. Since of its longer plasma half-life than T3, T4 is preferred for the treatment of hypothyroidism because it is simpler to regulate its plasma concentrations (4).

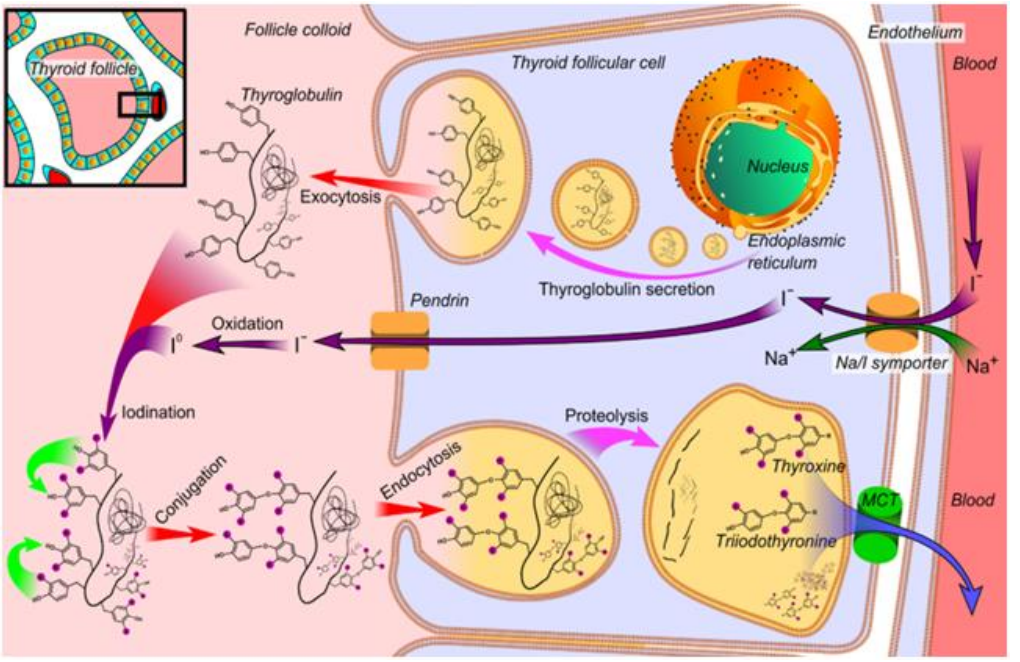

Fig 2 – Overview of the synthesis of thyroid hormones (Source – Google Images)

4. Common thyroid diseases in India

4.1 Hyperthyroidism

Hyperthyroidism can be caused by a wide range of disorders. The most prevalent cause of hyperthyroidism is Graves' disease, an autoimmune condition. As a result, the thyroid produces an excessive amount of hormone in response to the antibodies. Women are more likely than men to be affected by Graves' illness. Genetic evidence suggests that it is passed down from generation to generation. If you or a member of your family has a history of this disease, inform your doctor very away (5).

Hyperthyroidism can be caused by:

1. Overconsumption of Iodine, which is a critical component of T4 and T3
2. Inflammation of the thyroid gland, which causes T4 and T3 to seep from the gland, is known as thyroiditis
3. Ovaries or testes tumours
4. Thyroid or pituitary gland tumours that are not cancerous
5. High doses of dietary supplements or medication containing tetraiodothyronine

Signs and Symptoms of Hyperthyroidism

1. An unexplained drop in weight
2. Having a heightened sense of nervousness or excitement.
3. A pounding in the chest
4. Unsteadiness
5. Shivering
6. Frequently feeling overheated.
7. Red itchy skin

8. A greater number of bowel movements than is normal.
9. Hair thinning and thinning of the hair

4.2 Low thyroid hormone levels

Hypothyroidism is a condition in which the thyroid is underactive. This can occur at any age, although the likelihood grows with advancing years, and it is almost always the result of a hereditary condition. Hypothyroidism is three times as common in women than in men (6).

Hashimoto's thyroiditis, an autoimmune condition, and genetics are two of the most common causes of hypothyroidism.

Dietary restrictions on iodine intake.

Certain cancer, cardiac, and mental drugs might have side effects.

Thyroid surgery to remove the gland

Hypothyroidism is characterised by the following symptoms:

1. Unexpected weight gain or difficulty in shedding pounds
2. Fatigue
3. Depression
4. Alopecia areata (hair loss) with dandruff
5. Muscle aches and pains
6. Skin that is parched
7. Goitre (swelling of thyroid gland)
8. Nails that are too brittle.
9. Slow heartbeats
10. Periods of inconsistency
11. Cold sensitivity.
12. Constipation
15. Tendonitis in the wrist.

Thyroid enlargement, known as goitre, is common in many thyroid conditions and is associated with a wide range of symptoms. In order to boost thyroid hormone production, increased signalling to the thyroid via TSH receptors is a major contributor to this phenomenon. This results in an increase in the gland's size (hypertrophy) and an increase in blood flow. When the thyroid is underactive due to hypothyroidism or iodine insufficiency, the body responds by increasing the amount of thyroid stimulating hormone (TSH) released into the bloodstream. This increases the thyroid's ability to create thyroid hormone. Thyroid hormone synthesis increases as a result of this stimulation. There is an excess activation of the TSH receptor in the presence of normal thyroid hormone levels in Graves' disease or toxic multinodular goiter-induced hyperthyroidism. Thyroid hyperplasia can occur for a variety of reasons, including an inability of the thyroid gland to release thyroid hormones or thyroid hormone precursors, a defect in the thyroid's genetic makeup, or an increase in iodine intake from food, supplements, or medications (7).

A condition known as chronic lymphocytic thyroiditis or Hashimoto's disease, in which the thyroid gland is gradually damaged, is known as Hashimoto's thyroiditis. Symptoms may be unnoticed in the beginning. The thyroid may expand over time, resulting in a non-painful goitre. Hypothyroidism can cause a variety of symptoms, including weight gain, lethargy, constipation, depression, thinning hair, and general discomfort in some people. After a long period of time,

the thyroid's size tends to decrease. Thyroid lymphoma is a possible hazard. Genetic and environmental factors are known to play a role in Hashimoto's thyroiditis. A history of the disease in one's family or having another autoimmune disease increases one's risk. Blood testing for thyroid stimulating hormone (TSH), thyroid stimulating hormone (T4), and antithyroid autoantibodies confirm the diagnosis (8). Graves' illness and nontoxic nodular goitre can also cause similar symptoms. Levothyroxine is commonly used to treat Hashimoto's thyroiditis. Some doctors may advocate no treatment if hypothyroidism is not present, while others may recommend treating the goitre to lessen its growth. Pregnant women need to consume an adequate amount of iodine, but those who are afflicted should limit their intake.

Surgery to remove a goitre is rarely necessary.

The prevalence of Hashimoto's thyroiditis in Caucasians is approximately 5%. Between the ages of 30 and 50, it is most commonly seen in women, with men being significantly less likely to suffer from it. Symptoms of the condition are becoming more common. In 1912, Hakaru Hashimoto, a Japanese physician, reported it. It was diagnosed as an autoimmune disease in 1957. (9). Endocrine malignancies, such as thyroid cancer, are among the most prevalent cancers of the endocrine system. As a percentage of all cancers, it accounts for less than 1% of all endocrine cancers, yet it accounts for about 90% of endocrine cancer mortality (10). "nodules" are benign growths on the thyroid gland, and 90% of them are. Cancer is caused by malignant nodules. Based on the appearance of thyroid cancer cells under a microscope, there are four primary forms of thyroid cancer. Among them are: Thyroid cancer with papillary features Second, there is follicular thyroid cancer. 1) Medulloblastoma of the thyroid gland and 2) Anaplastic thyroid cancer. On the whole, the prognosis for thyroid cancer is very good, with high 10-year survival rates; nevertheless, the prognosis can vary depending on a specific subtype of thyroid cancer. Well-differentiated and poorly differentiated thyroid tumours are two of the most common types of thyroid cancer. Without treatment, they can spread to various regions of the body at varying speeds (11).

5. Thyroid Disorders Diagnosis

5.1 Blood Tests

A blood test is a quick and painless way to find out your health status. For the most conclusive diagnosis of a thyroid disease, blood testing are essential. If your thyroid isn't working properly, a blood test measures the amount of thyroid hormones in your blood. Blood is drawn from a vein in your arm for these tests (12). In order to determine whether or not the Patient have:

1. Hyperthyroidism.
2. Hypothyroidism.

Hyperthyroidism and hypothyroidism can be diagnosed with thyroid blood testing. Thyroiditis is one of the most common causes.

1. Graves' illness.
2. Hashimoto's Disease

3. Thyroiditis.
4. Goiter.
5. A nodule on the thyroid.
6. Cancer of the thyroid

It's possible you'll be subjected to one or more of the following blood tests:
When the pituitary gland produces thyroid-stimulating hormone (TSH), it regulates the levels of thyroid hormones in the bloodstream. This is the most common test used by healthcare providers to determine if your thyroid is out of whack. If you have hypothyroidism, your TSH level is likely to be increased. If you have hyperthyroidism, it's likely that your TSH level will be lower than normal. Measurement of thyroid hormones such as T4 and T3 may be done if the TSH level is abnormal to further investigate the issue. For an adult, the normal TSH level is between 0.40 to 4.50 mIU/mL.

To monitor treatment of thyroid problems, thyroxine tests are done for hypothyroidism and hyperthyroidism. Hypothyroidism is associated with low T4 levels, while hyperthyroidism is associated with high T4 levels. Adults should have T4 levels between 5.0 and 11.0 ug/dL. (micrograms per decilitre of blood). Method of measuring thyroxine that eliminates the binding impact of proteins that normally bind thyroxine and prevents proper measurement is known as free T4 (FT4). A healthy adult's FT4 level should fall anywhere in the range of 0.9–1.7 ng/dL. (nanograms per decilitre of blood). Hyperthyroidism can be diagnosed or the degree of hyperthyroidism assessed using triiodothyronine testing, or T3. Hypothyroidism can have low T3 levels, but this test is more typically used to diagnose and treat hyperthyroidism, which has increased T3 levels. 100 to 200 ng/dL of T3 is the normal range (nanograms per decilitre of blood). Triiodothyronine (T3) is an important hormone in the body, but it can be difficult to assess since it binds to protein, which can distort the results. FT3 concentrations range from 2.3 to 4.1 pg/mL in the normal range (picograms per millilitre of blood). If your healthcare provider suspects that you have a thyroid disease based on these tests, he or she may prescribe more testing to rule it out.

Blood tests may also include the following:
Thyroid antibodies: These tests are used to diagnose autoimmune thyroid diseases. C-cell hyperplasia and medullary thyroid carcinoma are both rare thyroid illnesses that can be diagnosed by a calcitonin test. Thyroiditis (thyroid inflammation) and thyroid cancer treatment can be monitored with a thyroglobulin test (14).

5.2 Testing for imaging

Looking at the thyroid can answer a lot of queries in many circumstances. A thyroid scan is a type of imaging examination that your healthcare provider may do. This gives your doctor a chance to examine your thymus for any changes in size, shape, or growth (nodules). An ultrasound is an anti-aging test that your doctor may also utilise. The reverberations are captured and used to create moving images on film or video. Even though you might associate ultrasounds with pregnancies, the truth is that they can be used to identify a wide range of health problems. Ultrasounds, in contrast to X-rays, do not make use of

radiation. Before your ultrasound, there is usually no need for any preparation. On the examination table, you will be asked to lay flat and with your head resting on an extra pillow, which will be used to tilt your head back. The region to be studied is covered with a heated, water-soluble gel. Using this gel will not harm your skin or ruin your clothing. Using a probe, your healthcare professional will next gently glide the probe around your neck to examine all areas of your thyroid. Typically, an ultrasound takes between 20 and 30 minutes (15).

5.3 Examining the body physically

Thyroid function can also be readily assessed during a routine physical examination at your doctor's office. This is a quick, non-invasive procedure in which your healthcare practitioner examines your neck for signs of thyroid tumours or enlargement (15).

6. Thyroid Disorders Treatment

Thyroid hormone production is inhibited by anti-thyroid medicines such as methimazole and propylthioracil. Treatment with radioactive iodine destroys thyroid cells and prevents the thyroid from producing excessive quantities of thyroid hormones, beta blockers and surgery are also the options (16).

Nanomedicines in thyroid disease treatment

The field of medicine known as "nanomedicine" makes use of the latest advances in nanotechnology to better diagnose and treat patients. Nanoparticles and nanorobots, as well as other nanoscale materials, are used in nanomedicine to diagnose, deliver, sense, or regulate in a living body. The median survival period for patients with the most aggressive form of thyroid cancer, anaplastic thyroid carcinoma (ATC), is three to five months. RNA interference (RNAi) nanotechnology is one potential technique for treating this and other solid tumours, but delivering RNAi medicines to tumour locations has proven difficult (17).

Targeting of the Thyroid Cancer Tumor Vascular System

During the process of angiogenesis, which involves the recruitment of new blood vessels from already-existing ones, tumours grow. One of the most important roles tumour vascularization plays in the evolution of cancer from a tiny localised mass to a much larger and more aggressive burden that can spread throughout the body is. The tumor's oxygen and nutrients are supplied via the newly created vascular, which increases the tumor's growth and spread potential. There are many ways to fight cancer by targeting the tumor's blood vessels. If the established vascular network is broken, it may lead the tumour cells' demise due to hypoxia and nutrition depletion (18).

As a result of these and other advantages, targeting the tumor's vascular supply over the tumour interstium is preferable to conventional treatments because it avoids the problem of getting drugs into tumours, which is a major problem for conventional treatments; the endothelial cells are not transformed and are not

likely to develop mutations that lead to drug resistance, and the death of the endothelial cells is preferable to conventional treatments because it avoids the problem of getting drugs into tumours, which is a major problem for conventional treatments. Antivascular therapy, on the other hand, focuses on the endothelium cells rather than the cancer cells. Because of the concentration of negatively charged proteoglycans (heparan sulphate), endothelial cells lining tumour blood arteries can proliferate considerably quicker than endothelial cells in quiescent tissues. Drug carrier molecules with positively charged or cationic charge can readily bind to these anionic molecules on the tumour vasculature. Liposomal medication delivery has been the most widely used method for targeting the vasculature (19).

Liposomes:

Liposomes are used in medication delivery and those are an important class of pharmacological carriers. Natural or synthetic lipid bilayers are sandwiched together to produce spherical, self-assembling structures. Inside and between the lipid bilayers, liposomes contain an aqueous core. Depending on the drug's qualities and the encapsulation technique, they can either encapsulate it in an aqueous core or a bi-layer. Stealth liposomes are formed when polymers like polyethylene glycol (PEG) are introduced into liposomes. Because the reticuloendothelial system clears sterically stabilised liposomes at a slower rate than ordinary liposomes, they remain in circulation for longer (RES). Liposomes offer various advantages since they are biocompatible and nonimmunogenic. Physical features including size, charge, membrane rigidity and stability may be easily adjusted; the medications contained within are shielded from the inactivating effects of conditions and avoid untimely drug release by these physicochemical characteristics. The phospholipid vesicles have an ability to deliver medications to specific intracellular targets (20).

Induced Resonance Imaging:

When chemotherapy medicines are coupled with magnetic nanoparticles (ferrofluids), an external magnetic field exists is created at the tumour location to distribute the chemotherapeutic chemicals. Using an external magnetic field, a pharmaceutically stable formulation containing the medicine and magnetic particles can be retained in place at the target site (or tumour). As a result, there is less risk of the drug accumulating in healthy tissues as a result of this method of delivery. The total amount of drug taken up by the RES is decreased as a result of both better target selectivity and prolonged drug exposure to the target. Medication efficacy and toxicity are greatly improved by MDT's use of significantly lower dosages of drug (21).

Ferrofluids:

When single-domain magnetic particles are disseminated in either a polar or non-polar liquid carrier, the result is a magnetic colloid, also known as a ferrofluid. Nanoparticles' biocompatibility and toxicity can be determined by the type of the magnetically responsive component (e.g. iron or nickel), as well as their final core and coating size. These features are critical in determining whether the

nanoparticles are safe for human use. Magnetite (Fe3O4) and maghemite (-Fe2O3) are the most often used iron oxide particles in biological applications. They are highly magnetic, poisonous, and prone to oxidation, therefore they are of little interest to chemists and researchers. In the absence of an external magnet, iron oxide nanoparticles are superparamagnetic; that is, they have a magnetic moment when an external magnet is applied (22).

Magnetized liposomes:

They can be made by encasing ferrofluids inside the liposomal core. Alternatively, they are made up of magnetic nanoparticles that have been coated with a phospholipid bilayer. Magneto liposomes are a promising vehicle for the passive administration of magnetic nanoparticles as therapeutic agents. Incorporating magnetic particles into liposomes provides further protection against aggregate formation and oxidation, which is an advantage. It is possible to encapsulate medications or genes with magnetite simultaneously in magnetic liposomes like normal liposomes, which has the same biokinetic and structural advantages. Additionally, the surface of these nanoparticles can be chemically altered to target particular tissues (23).

7. Conclusion

Most efforts aimed at achieving targeted and site-specific medication delivery are now focused on nanoparticles. Size, surface charge, surface modification and hydrophobicity all influence the capacity of nanoparticles to target certain molecules and ion channels. Selective binding, targeted delivery, and toxicity are all issues that need to be addressed. Lack of information on nanoparticle toxicity is a key topic that need further attention. As long as these nanoparticles are developed with care, they could help usher in a new paradigm in medicines and research. Research on nanoparticle synthesis using supercritical fluids, which are environmentally safe and free of harmful solvents, is the most promising in the field. Nanoparticle-based drug delivery is currently undergoing extensive research in order to overcome these challenges and become the gold standard for site-specific treatments.

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