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REVIEW

Theranostic Potentials of Metallic Nanoparticles in Thyroid Diseases: Challenges and Prospects

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Abstract: Thyroid disorders, encompassing benign nodules, goiter, hyperthyroidism, hypothyroidism, and malignancies, present significant clinical challenges due to limitations in conventional diagnostic and therapeutic modalities. Metallic nanoparticles, particularly gold and iron-oxide-based systems, have emerged as promising theranostic agents, enabling simultaneous disease diagnosis and targeted therapy. This review examines recent advancements in the application of metallic nanoparticles across the spectrum of thyroid diseases. It highlights their roles in enhancing imaging modalities such as ultrasound, MRI, and CT, as well as their therapeutic potential through photothermal ablation, magnetic hyperthermia, and controlled drug delivery. Comparative analysis of nanoparticle physicochemical properties, targeting strategies, in vitro and in vivo efficacies, and translational feasibility is presented. Furthermore, the review addresses current challenges, including biocompatibility, toxicity, biodistribution, and regulatory considerations. Emerging approaches involving stimuli-responsive nanoparticles and artificial intelligence-driven imaging are discussed as future directions. This comprehensive synthesis underscores the transformative potential of metallic nanoparticle-based theranostics in thyroid disease management, advocating for interdisciplinary collaboration to facilitate clinical translation.

Keywords: thyroid disorders, metallic nanoparticles, theranostics, nanomedicine, photothermal therapy, magnetic hyperthermia

Introduction

The thyroid gland is a small, butterfly-shaped endocrine organ located in the anterior neck, just below the larynx and wrapped around the trachea. It comprises two lobes connected by an isthmus and is composed microscopically of thyroid follicles, spherical units lined by follicular epithelial cells, which synthesize and secrete hormones.[1] It produces two primary thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), which regulate metabolism, growth, energy expenditure, protein synthesis, and neurocognitive development in children. It also secretes calcitonin, which plays a role in calcium homeostasis.[2] Hormone release is regulated by the hypothalamic–pituitary–thyroid axis: the hypothalamus secretes TRH, which stimulates the pituitary to release TSH, which in turn prompts the thyroid to secrete T_3 and T_4, with negative feedback control.[3] As the earliest endocrine gland to develop embryonically, the thyroid originates from endodermal tissue and plays a vital role throughout life in both physiological and developmental contexts.[4] Thyroid disorders, including functional abnormalities like hyperthyroidism and hypothyroidism, structural issues such as goiter and nodules, and malignant changes like thyroid cancer, are among the most common endocrine diseases. Recent epidemiological analyses indicate more than 1.6 billion individuals are at risk of thyroid dysfunction, primarily due to iodine deficiency and autoimmune causes.[5–7] This rise is especially pronounced in women and in regions with higher sociodemographic indices, underscoring the growing global health and economic impact of thyroid disease.[8] The global incidence of thyroid cancer alone has been steadily rising, with papillary thyroid carcinoma accounting for approximately 85% of cases.[9] Concurrently, autoimmune thyroid diseases like Graves' disease and Hashimoto's thyroiditis contribute substantially to the burden of hyper- and hypothyroidism, respectively. These

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disorders not only impair metabolic homeostasis but also considerably diminish quality of life and may lead to life-threatening complications if inadequately managed.[10]

Despite advances in diagnosis and management, clinical limitations persist in this area. Current diagnostic modalities for thyroid diseases predominantly rely on ultrasound imaging (USG), fine-needle aspiration cytology (FNAC), and nuclear scintigraphy using radioisotopes such as iodine-123 or technetium-99m. While these techniques are widely used, they exhibit limitations in specificity and sensitivity, particularly in differentiating benign from malignant lesions or in detecting residual or recurrent disease post-treatment.[11] Therapeutic interventions, including surgery, radioiodine therapy, and pharmacologic management, have advanced considerably but remain challenged by incomplete tumor resection, radioiodine resistance, adverse effects, and the need for lifelong hormone replacement in hypothyroidism (Figure 1). These clinical limitation underscores the demand for precision theranostics for combining targeted imaging with localized treatment.[12]

In recent years, the concept of theranostics, which integrates therapeutic and diagnostic capabilities into a single platform, has gained prominence, especially in oncology and endocrinology.[14,15] Metallic nanoparticles (MNPs), including gold (AuNPs), silver (AgNPs), and iron-oxide nanoparticles (IONPs), offer distinct advantages over conventional nanomedicine platforms due to their unique optical, magnetic, and plasmonic properties that enable multimodal imaging, photothermal ablation, and magnetic hyperthermia in a single construct[16] (Figure 2). MNPs offer superior stability as compared to polymeric or lipid-based nanocarriers, tunable surface chemistry, and enhanced signal contrast across MRI, CT, facilitating early lesion detection and image-guided therapy.[17–19] These properties facilitate enhanced imaging contrast across modalities such as ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT), alongside enabling therapeutic interventions including photothermal therapy (PTT), magnetic hyperthermia, and controlled drug release.[20,21] Gold nanoparticles (AuNPs) exhibit localized surface plasmon resonance (LSPR), making them highly effective contrast agents for imaging and efficient mediators of photothermal ablation, which can selectively

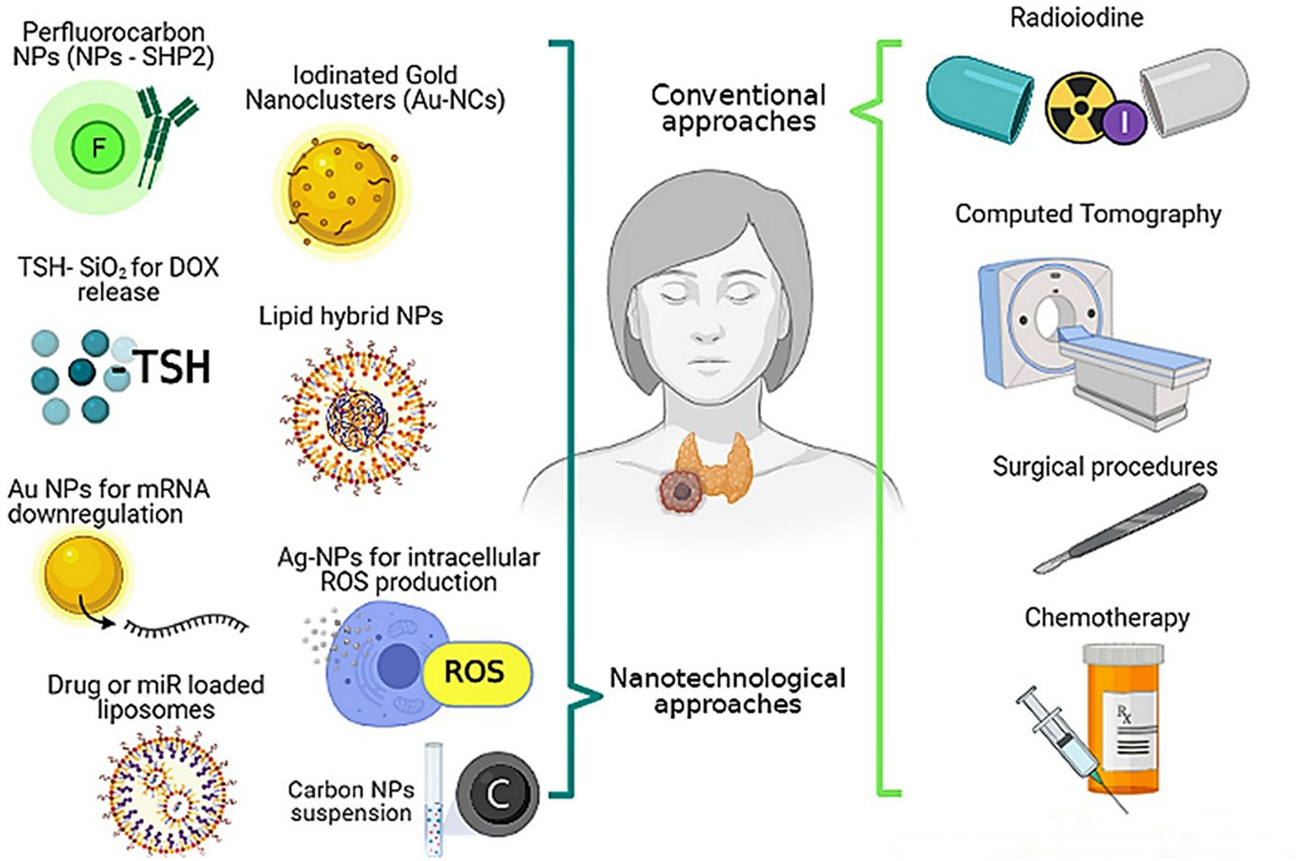

Figure 1 Schematic representation of the advantages of metallic nanomaterials in thyroid theranostics. Adapted with permission from Reference.[13]

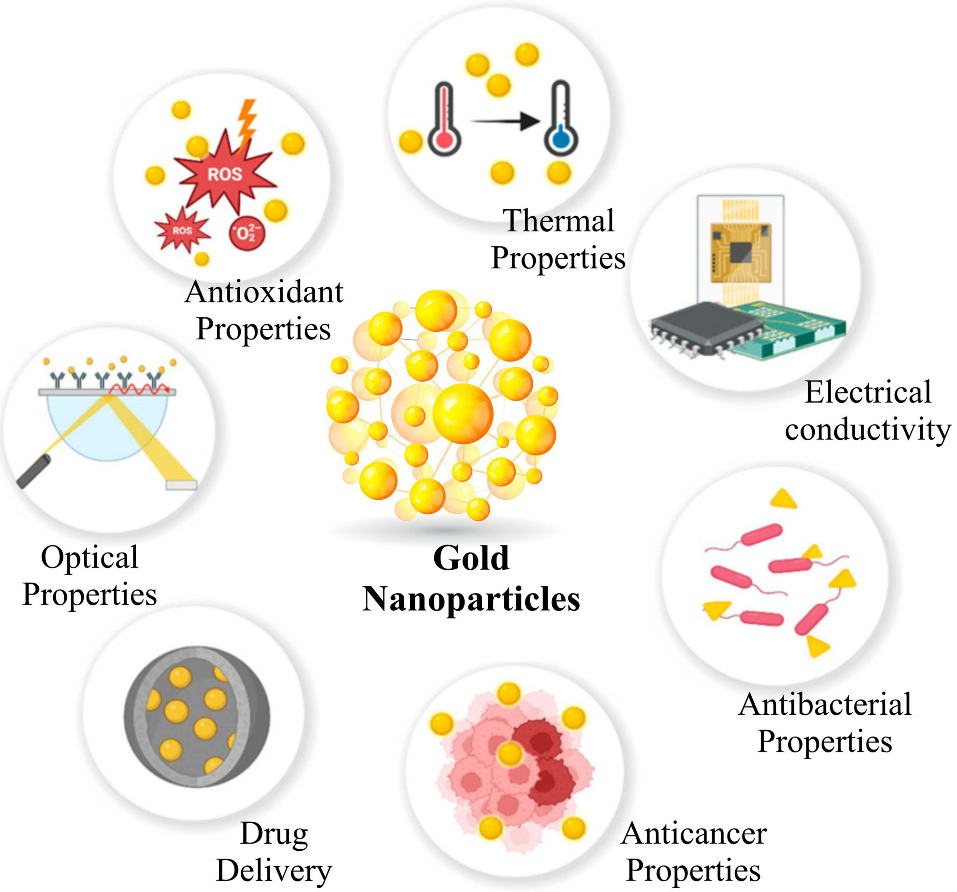

Figure 2 Key applications of gold nanoparticles across biomedical domains. Their unique physicochemical traits, strong localized surface plasmon resonance (LSPR), high biocompatibility, low toxicity, and ease of surface functionalization enable their use in imaging, biosensing, and cancer therapy, including as effective radiosensitizers. The figure is made by the authors themselves.

destroy diseased thyroid tissue.[22] Superparamagnetic iron-oxide nanoparticles (IONPs), predominantly Fe_3O_4-based, offer T_2-weighted MRI contrast through superparamagnetism and enable localized magnetic hyperthermia (MH) upon exposure to alternating magnetic fields, inducing precise tumor ablation via heat generation while minimizing systemic impact.[23] Their inherent magnetic properties also support targeted drug delivery and catalysis in tumor microenvironments. Composite architectures that fuse gold with iron-oxide (core–shell Fe_3O_4@Au or Janus designs) synergize imaging and therapy: the iron-oxide core enhances MRI and MH, while the gold shell adds CT contrast and NIR-mediated photothermal therapy (PTT), allowing dual-mode thermal treatment through both magnetic and optical triggers. In vivo studies demonstrate that Fe_3O_4/Au nanohybrids swiftly elevate tumor temperatures (~20 °C rise within 2 minutes) under combined alternating magnetic field and NIR stimulation, confirming enhanced heat dissipation and superior tumor ablation compared to either modality alone.[24] Hybrid nanoparticles represent a flexible theranostic platform, supporting multimodal imaging (MRI/CT/optical), targeted hyperthermia, and controlled drug release, making them highly promising candidates for enhanced, image-guided thyroid cancer therapy.[24–26]

Given these multifaceted capabilities, metallic nanoparticles offer a versatile platform that addresses many of the current challenges in thyroid disease management.[27] This review systematically synthesizes literature published from 2020 onward, encompassing the diagnostic and therapeutic potentials of metallic nanoparticles across the spectrum of thyroid disorders, including benign, functional, and malignant pathologies. In the following sections, we will examine the suitability of specific nanoparticle types for different thyroid diseases, evaluating their physicochemical properties, targeting strategies, efficacy, and translational prospects.

Nanoparticle-Based Theranostics: Targeted Strategies for Diverse Thyroid Diseases

This section provides a comprehensive classification of metallic nanoparticles based on their diagnostic and therapeutic roles in different thyroid diseases, highlighting recent advances and disease-specific applications.

Benign Nodules and Goiter

Benign thyroid nodules and goiter represent the most prevalent thyroid abnormalities, affecting up to 50% of the adult population in iodine-deficient regions.[28] It typically arises from dysregulated follicular cell proliferation, often driven by iodine deficiency, growth factor imbalances, or chronic inflammation, resulting in localized hyperplasia or hypertrophy. Current imaging modalities, such as conventional ultrasound, lack sufficient specificity to reliably differentiate benign from malignant lesions or assess treatment efficacy.[29,30] Gold nanoparticles (AuNPs), owing to their tunable surface plasmon resonance, have demonstrated significant potential in enhancing ultrasound contrast for thyroid nodule characterization.[31] Functionalization of AuNPs with thyroid-specific ligands, such as thyroglobulin antibodies, enables targeted accumulation within nodular tissues, thus improving image resolution and diagnostic accuracy. For instance, recent studies report that AuNP-enhanced ultrasound achieved a sensitivity increase of 20% compared to standard methods in ex vivo thyroid specimens.[32]

Magnetic nanoparticles, particularly iron-oxide nanoparticles (IONPs), offer an alternative modality by facilitating localized hyperthermia ablation of nodular tissues. When subjected to an alternating magnetic field, IONPs generate heat sufficient to induce apoptosis in hyperplastic cells via enhanced reactive-oxygen species (ROS) generation and lysosomal membrane permeabilization without damaging surrounding normal tissue. Preclinical rodent models have validated the efficacy of magnetic hyperthermia in reducing nodule volume by up to 60% within two weeks post-treatment.[33] Hybrid nanoparticles combining gold and iron oxide cores merge diagnostic imaging and therapeutic functionalities into a single platform. Such composites enable simultaneous ultrasound and magnetic resonance imaging (MRI) with concurrent photothermal and magnetic hyperthermia ablation.[16] A recent open-access study demonstrated that hybrid NPs significantly reduced nodular volume while enabling real-time imaging-guided therapy. These advancements represent a paradigm shift in minimally invasive management of benign thyroid disease, emphasizing the integration of diagnosis and therapy. Translational considerations, including heat generated by IONPs or hybrid systems, must be carefully calibrated to reliably induce apoptosis (rather than necrosis) in thyroid nodular tissue while preserving adjacent thyroid parenchyma and critical structures like the laryngeal nerve and trachea. The fate of nanoparticles (biodegradation, clearance, immune responses, and potential off-target accumulation in organs) must be addressed; for example, recent work showed alterations in hepatic enzyme function after MRI-contrast IONPs in animal models.[34] Theranostic potential in benign conditions, the subsequent section explores metallic nanoparticle applications in hyperthyroidism, including Graves' disease and toxic nodules.[24,35]

Hyperthyroidism (Graves' Disease, Toxic Nodules)

Hyperthyroidism, such as Graves' disease and toxic nodules, pathogenesis involves autoimmune stimulation of the thyroid-stimulating hormone receptor (TSHR), leading to excessive thyroid hormone synthesis and secretion (Figure 3).[36–38] Graves' disease is characterized by autoantibodies that mimic TSH, inducing diffuse glandular hyperactivity, whereas toxic nodules exhibit constitutive activation of intracellular signaling pathways independent of TSH regulation.[38] Graves' disease, an autoimmune hyperthyroidism, and toxic nodular goiter are principal etiologies requiring targeted intervention. Traditional treatment modalities such as antithyroid drugs, radioiodine therapy, and surgery have limitations, including adverse effects, recurrence, and hypothyroidism induction.[39,40]

Graves' disease is an autoimmune hyperthyroid disorder characterized by autoreactive T and B lymphocyte infiltration and the production of TSH receptor–stimulating antibodies (TSHR-Ab), which mimic TSH and drive excessive thyroid hormone synthesis. Antigen-presenting cells (APCs) initiate T cell activation via MHC–antigen presentation and CD40–CD40L interactions, further propagating inflammation through cytokines such as IFN-γ, TNF-α, and interleukins. These immune responses lead to diffuse glandular hyperactivity. This pathogenic cascade presents multiple potential

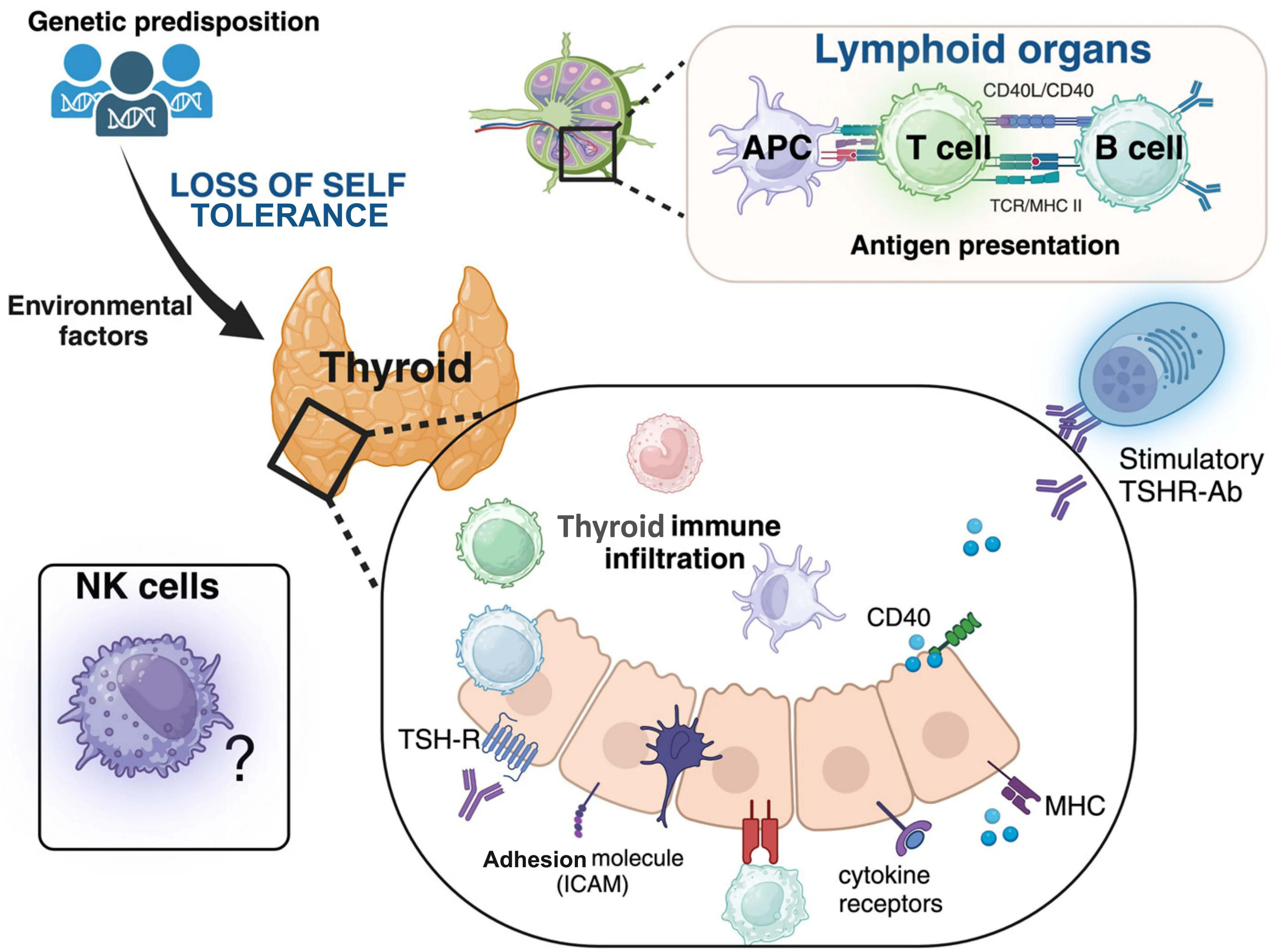

Figure 3 Schematic representation of the immunopathogenesis of Graves' disease in the context of theranostic targeting. Adapted from the reference[41] under the terms and conditions of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

targets for metallic nanoparticle–based theranostics. Gold nanoparticles (AuNPs), conjugated with TSHR antibodies, enable targeted photothermal ablation of hyperfunctioning thyroid tissue, while iron oxide nanoparticles (IONPs) facilitate magnetic hyperthermia under an external alternating field. Combinatorial nanoparticle strategies may enhance selectivity and therapeutic efficacy in hyperthyroid disorders such as Graves' disease and toxic nodular goiter.

Gold nanoparticles have been investigated extensively for their targeted photothermal therapeutic (PTT) applications in hyperthyroid tissue ablation. The LSPR properties of AuNPs facilitate efficient conversion of near-infrared (NIR) light into localized heat, enabling selective destruction of hyperfunctioning thyroid cells. Surface conjugation with thyroid-stimulating hormone receptor (TSHR) antibodies enhances nanoparticle specificity, minimizing collateral damage. In a recent preclinical trial, AuNP-mediated PTT achieved a 75% reduction in thyroid hormone levels in hyperthyroid rat models within 72 hours, demonstrating rapid therapeutic efficacy. Heat raises intracellular temperature to 43–47°C, initiating HSP (heat shock protein) suppression, membrane disruption, mitochondrial dysfunction, and ultimate apoptotic cell death.[13,42,43] Iron oxide nanoparticles have been similarly employed in magnetic ablation strategies. Under an external alternating magnetic field, IONPs accumulate in hyperactive thyroid nodules and generate cytotoxic hyperthermia, offering a non-invasive alternative to surgery.[44,45] Emerging studies also investigate combinatorial approaches where AuNPs and IONPs are co-administered to harness dual photothermal and magnetic hyperthermia effects, potentially overcoming limitations of monotherapy. These preclinical findings underscore the translational potential of metallic nanoparticle theranostics in hyperthyroid disorders.[46,47]

Hypothyroidism (Hashimoto's Thyroiditis)

Hypothyroidism often stems from autoimmune destruction, as observed in Hashimoto's thyroiditis, where lymphocytic infiltration leads to gradual follicular cell apoptosis and reduced hormone production. Chronic inflammation and fibrosis contribute to progressive glandular failure.[30,48] Lifelong oral levothyroxine supplementation remains the standard of care, yet challenges persist, including variable absorption, compliance issues, and fluctuating serum hormone levels. Nanoparticle-based drug delivery systems offer a promising avenue for controlled, sustained release formulations to overcome these hurdles.[49] Polymeric nanoparticles encapsulating levothyroxine have demonstrated improved bioavailability and prolonged therapeutic effects in animal models. For example, chitosan-coated AuNPs loaded with levothyroxine exhibited sustained drug release over 72 hours with enhanced intestinal uptake in rats, suggesting improved oral delivery efficiency. Further, iron/gold hybrid nanoparticles functionalized with inflammation-targeting ligands have been investigated for non-invasive imaging of residual thyroid tissue and monitoring of autoimmune inflammation using combined MRI and photothermal imaging modalities.[50]

Beyond endocrine regulation, chronic or inadequately managed hypothyroidism exerts significant systemic effects, particularly on skeletal health, as depicted in Figure 4. In adults, diminished thyroid hormone activity disrupts normal bone remodeling processes, while in pediatric populations, it can impede ossification and impair skeletal development.[51,52] Recent advances suggest that metallic nanoparticles hold promise not only in enhancing hormone replacement strategies but also in targeting bone-specific molecular pathways, including thyroid hormone receptors (TRs) and the RANK/RANKL/OPG axis, for both diagnostic and therapeutic applications. Moreover, stimuli-responsive nanocarriers capable of releasing hormones in response to physiological cues local pH variations or inflammatory markers, are being actively investigated as part of a personalized approach to hypothyroidism management. Although

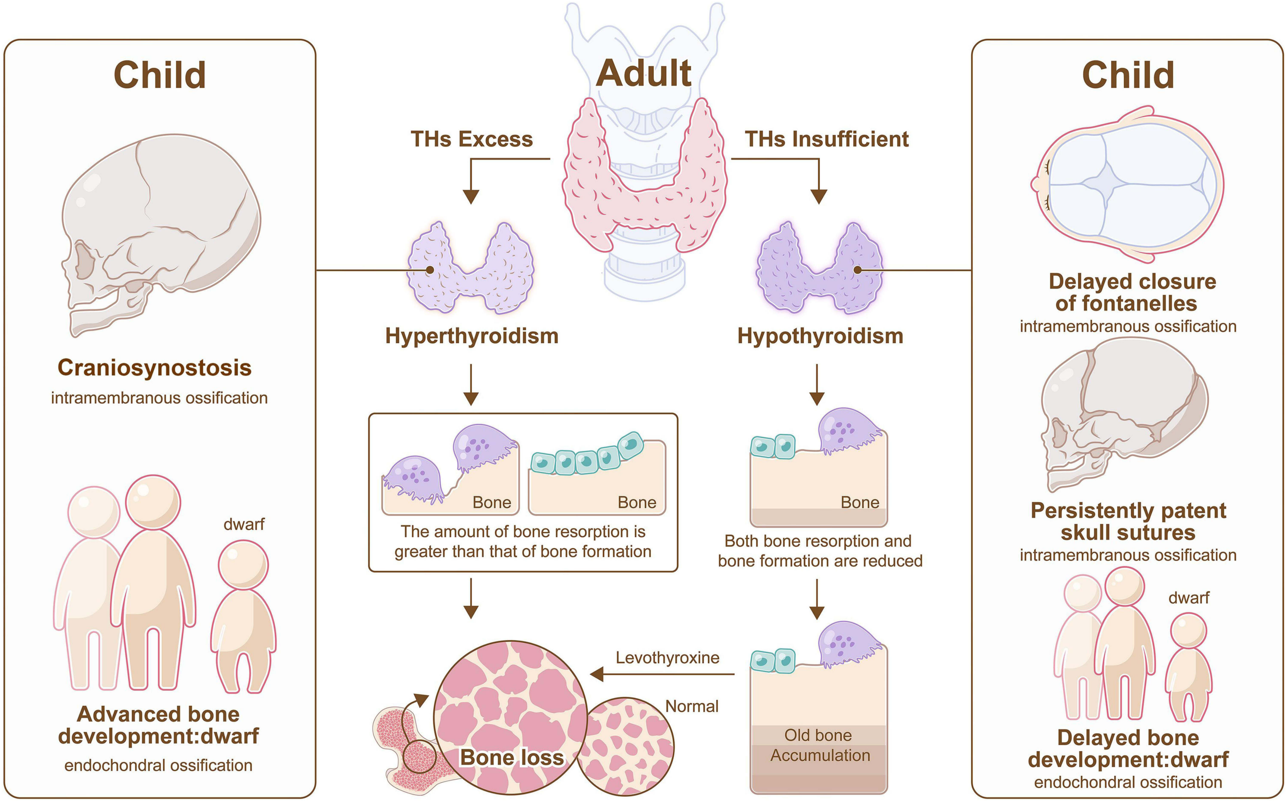

Figure 4 Skeletal effects of thyroid dysfunctions. In adults, hyperthyroidism induces bone loss via increased resorption, while hypothyroidism impairs remodeling; LT4 therapy may further contribute to loss. In children, hypothyroidism delays ossification, whereas hyperthyroidism causes craniosynostosis and stunted growth. These alterations involve targets such as thyroid hormone receptors (TRs), RANK/RANKL/OPG pathway, MMPs, and bone turnover markers, highlighting potential sites for metallic nanoparticle–based theranostic intervention in thyroid-related bone disorders. Adapted from the reference[52] under the terms and conditions of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). Copyright© 2022 Zhu, Pang, Xu, Chen, Zhang, Wu and Gao.

these technologies remain in early developmental stages, they underscore the expanding potential of metallic nanoparticles in addressing a broader spectrum of thyroid-related dysfunctions beyond malignancies.[13,53]

Thyroid Cancer

Thyroid cancer is the most prevalent malignant neoplasm of the cervical region and endocrine system, characterized by a discernible upward trend in incidence over recent years.[54,55] Anaplastic thyroid cancer, characterized by high malignancy and aggressiveness, remains an unmet clinical need with no effective treatments available. Thyroid malignancies, including papillary, follicular, and anaplastic carcinomas, originate from genetic mutations affecting oncogenes (BRAF, RAS) and tumor suppressors (p53), driving uncontrolled cellular proliferation, invasion, and resistance to apoptosis.[56,57] Tumor microenvironment factors such as hypoxia and immune evasion further complicate disease progression. Thyroid cancer, particularly papillary and anaplastic variants, demands precise diagnostic and therapeutic strategies due to variable prognosis and treatment resistance.[58]

Circulating biomarkers have emerged as powerful tools for the non-invasive detection and monitoring of thyroid cancer (TC), facilitated by advancements in liquid biopsy and nanotechnology.[59] Among various nanomaterials, gold nanoparticles (AuNPs) are the most widely utilized due to their versatile signal enhancement capabilities across fluorescence, colorimetry, photoacoustics, surface-enhanced Raman scattering (SERS), electrochemical methods, dynamic light scattering (DLS), and localized surface plasmon resonance (LSPR).[60] For thyroid-stimulating hormone (TSH) detection, anti-TSH antibody-conjugated horseradish peroxidase (HRP) immobilized on platinum nanoparticles demonstrated chemiluminescent detection with a threefold faster response and 100-fold greater sensitivity than commercial kits. Similarly, dendrimer-enhanced gold electrodes have enabled ultrasensitive TSH detection down to 0.026 mIU/L, outperforming the standard third-generation immunoassays (~0.02 mIU/L sensitivity), although further sensitivity is not routinely required in clinical settings. For thyroglobulin (Tg), a biomarker critical for post-treatment surveillance, a novel fluoroimmunodiagnostic nanoplatform using tannylated ferritin nanocages achieved a detection limit of 4.3 pg/mL, surpassing conventional assays such as Elecsys Tg II. Likewise, for medullary thyroid cancer, calcitonin detection has been enhanced using FRET-based AuNP thin films and graphene oxide-modified electrodes, achieving limits of detection as low as 0.7 pg/mL, markedly lower than most commercial platforms. Detection of genetic mutations, particularly BRAF V600E and KRAS exon 2, is also facilitated by nanotechnology.[61] Circulating tumor DNA (ctDNA) and tumor cells can be isolated using magnetic nanoparticles (Fe_3O_4-based ferrofluids), with digital PCR achieving mutation detection limits as low as 0.0005%. Metallic nanoparticles, especially gold-based, have been extensively investigated for their theranostic capabilities in thyroid oncology. Surface-enhanced Raman spectroscopy (SERS) utilizing AuNPs enables ultra-sensitive detection of thyroid cancer biomarkers in serum and tissue samples, facilitating early diagnosis. Furthermore, AuNPs provide enhanced contrast in CT and MRI scans, improving tumor delineation. Therapeutically, AuNP-mediated photothermal therapy (PTT) achieves selective tumor ablation with minimal invasiveness. Radiosensitization effects of gold nanoparticles further potentiate radiotherapy outcomes by increasing DNA damage in cancer cells.[62–65] In vivo imaging and theranostics for thyroid cancer (TC) integrate conventional modalities with nanoparticle-enhanced techniques to improve detection depth, specificity, and treatment efficacy. Standard imaging tools ultrasound, CT, MRI, and radionuclide scans using ^131/123I with SPECT-CT, remain foundational for staging and monitoring residual disease, while FDG-PET's utility is less definitive.[66]

For medullary thyroid carcinoma (MTC), PET tracers like [^18F]-FDOPA and [^68Ga]-DOTATOC are preferred due to their superior sensitivity in neuroendocrine tissues.[67] However, superficial thyroid tumors located just beneath the skin can benefit from imaging strategies optimized for limited penetration depths: NIR-based photothermal imaging and ultrasound both have tissue penetration limits (~2–3 cm for NIR, 3–6 cm for unfocused ultrasound at 2.5 MHz). These modalities are enhanced by gold nanoparticle (AuNP) contrast agents, enabling dual-mode CT/NIR fluorescence imaging.[68] Mouse studies using BSA-coated, iodinated AuNP nanoclusters have detected thyroid tumors as small as ~2 mm^2. Similarly, ^131I-labeled mesoporous silica nanoparticles (MSNs) targeting VEGF delivered clear SPECT signals following intratumoral injection, though systemic delivery faced rapid phagocytic clearance via the mononuclear phagocyte system. Low-intensity focused ultrasound (LIFUS) offers combined imaging and therapy for superficial tumors; when paired with phase-changeable, antibody-decorated PLGA nanoparticles (eg, SHP2-targeted) and contrast

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agents, LIFUS can both visualize and induce tumor-selective damage without harming adjacent tissue.[69] Theranostic copper sulfide nanoparticles, PEG-coated,^64Cu-labeled CuS NPs, have been successfully used for PET-guided photothermal therapy (PTT) in anaplastic thyroid cancer (ATC) mouse models. Despite ~6% tumor accumulation post-injection, combined radiotherapy and NIR irradiation achieved tumor shrinkage of up to 83%, with no systemic toxicity. Similarly, polymeric NIR-emitting nanoparticles co-loaded with BRAF-silencing siRNA have been shown to both image BRAF-mutant xenografts and suppress tumor growth and metastasis in orthotopic mouse models. These "theranostic" platforms allow the spatial integration of diagnostics (imaging) and therapeutics (photothermal, gene silencing), although translation into clinical practice remains contingent upon the discovery of highly specific thyroid cancer markers and simplification of complex NP formulations. When available, patient-specific protein–corona profiling may help identify such markers and further personalize nanoparticle-assisted diagnosis.[61] Magnetic nanoparticles, predominantly iron oxide, complement these approaches through MRI contrast enhancement and magnetic hyperthermia treatments (Figure 5). In papillary thyroid carcinoma models, IONP-induced hyperthermia significantly decreased tumor volume and inhibited metastasis. Composite nanoparticles integrating gold and iron-oxide cores have demonstrated synergistic effects, enabling multimodal imaging and combination therapy in both papillary and anaplastic thyroid cancer models. These platforms underscore a shift toward personalized, minimally invasive oncology management, although challenges in nanoparticle biodistribution, toxicity, and regulatory approval persist.[70,71]

Theranostic copper sulfide nanoparticles (CuS NPs), specifically PEG-coated and ^64Cu-labeled, have emerged as a promising dual-functional platform for the diagnosis and treatment of anaplastic thyroid cancer (ATC). These nanoparticles serve as both positron emission tomography (PET) imaging agents and photothermal therapy (PTT) mediators. Their synthesis involves incorporating ^64Cu directly into the CuS matrix during preparation, eliminating the need for external chelators and enhancing their stability and imaging efficacy. In preclinical studies, these CuS NPs demonstrated significant tumor accumulation and retention, facilitating effective PET imaging. Upon near-infrared (NIR) laser irradiation, they induced localized hyperthermia, leading to substantial tumor cell apoptosis and necrosis. Combined

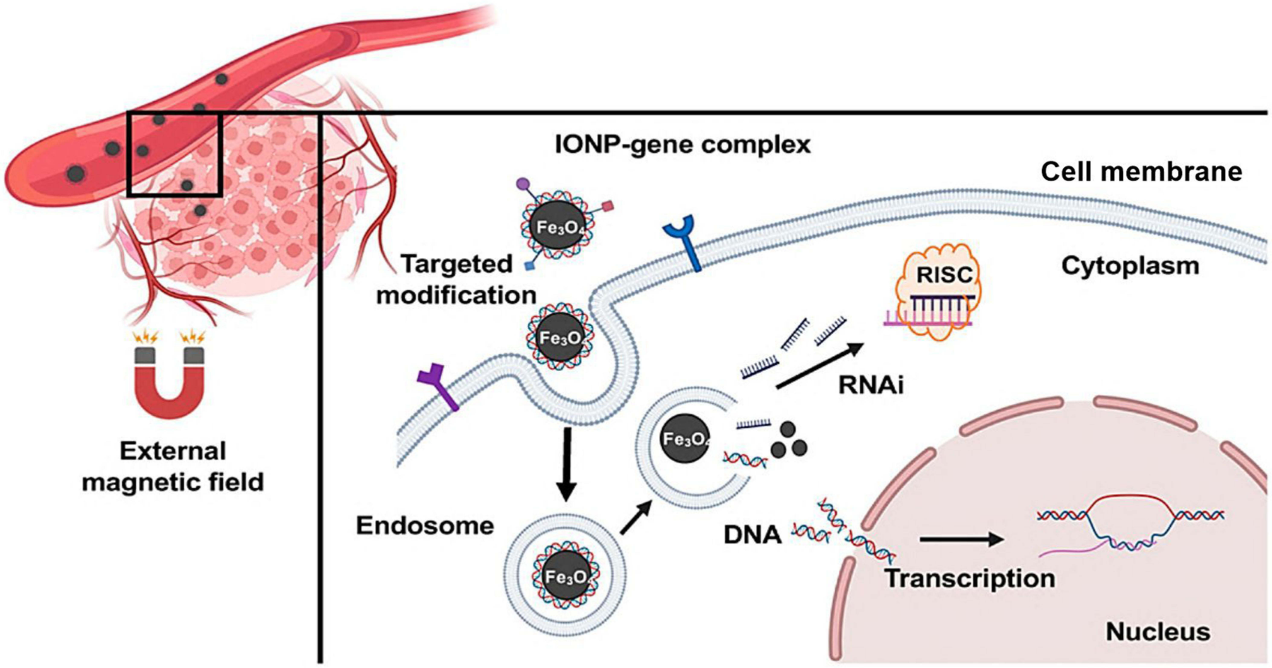

Figure 5 Schematic illustration of iron-oxide nanoparticles (IONPs) utilized for targeted gene delivery and tumor localization. This theranostic approach highlights IONP-mediated MRI contrast enhancement and magnetic hyperthermia, which have shown efficacy in reducing tumor volume and metastasis in papillary thyroid carcinoma models. Composite nanoparticles combining gold and iron oxide cores enable synergistic effects, supporting multimodal imaging and combination therapy in both papillary and anaplastic thyroid cancers. This strategy exemplifies a personalized and minimally invasive oncology paradigm, despite existing challenges in nanoparticle biodistribution, toxicity, and clinical translation. Adapted from the reference[72] under the terms and conditions of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

treatment with radiotherapy and NIR-induced PTT resulted in up to 83% tumor shrinkage without evident systemic toxicity. These findings underscore the potential of PEG-[^64Cu]CuS NPs as a versatile theranostic tool, offering precise imaging capabilities alongside targeted therapeutic effects, enhancing the clinical management of ATC.[73]

Comparative Analysis of Nanoparticle Platforms Across Thyroid Disorders

To comprehensively evaluate the translational potential of metallic nanoparticles in thyroid diseases, this section presents a side-by-side comparison of nanoparticle types, functionalization strategies, and disease-specific outcomes. Using data derived from recent preclinical and clinical research, diagnostic and therapeutic capabilities, and advancement toward clinical application are discussed in Table 1.

Metallic nanoparticles vary in function across thyroid disorders, showing distinct imaging and therapeutic roles. To assess their clinical relevance, Table 2 outlines the current translational status, including preclinical outcomes and early-stage human trials.

Recent advances in metallic nanoparticles highlight that AuNPs offer tunable size, strong plasmonic properties, and facile surface modification, enabling high-contrast imaging and photothermal therapy. IONPs, by contrast, provide intrinsic superparamagnetism for MRI, magnetic hyperthermia, and targeted drug delivery. A comparative summary of their physicochemical characteristics and clinical challenges is presented in Table 3.

Table 1 Overview of Metallic Nanoparticle Platforms Used Across Different Thyroid Disorders, Detailing Nanoparticle Type, Targeting Strategy, Imaging and Therapeutic Functionalities, and Outcomes Observed in in vitro and in vivo Models

Disorder	NP Type	Targeting Ligands	Imaging Modality	Therapy Type	Key in vitro/in vivo Outcomes	Ref.
Benign Nodules	Gold NPs	Thyroglobulin antibody	Ultrasound (enhanced US)	None/Contrast agent	Improved US contrast; increase in diagnostic accuracy ex vivo	[74]
Benign Nodules	Iron Oxide NPs	Passive accumulation	MRI	Magnetic hyperthermia	60% nodule volume reduction in rodent models (in vivo)	[75]
Benign Nodules	Au-Fe3O4 Hybrid NPs	Dual targeting (thyroid + tumor)	US + MRI	Combined thermoablation	Effective imaging-guided ablation; reduced nodule size in vivo	[76]
Hyperthyroidism	Gold NPs	TSH receptor antibody	NIR photothermal imaging	Photothermal therapy (PTT)	75% hormone reduction in hyperthyroid rat model (in vivo)	[32,77]
Hyperthyroidism	Iron Oxide NPs	Passive	MRI	Magnetic hyperthermia	Controlled thyroid ablation with minimal systemic toxicity	[78]
Hypothyroidism	Gold NPs (drug loaded)	None (oral delivery)	None	Sustained levothyroxine delivery	Improved bioavailability and controlled release (in vivo rat)	[79]
Hypothyroidism	Au-Fe hybrid NPs	Inflammation targeting ligands	MRI + photothermal	Imaging inflammation	Enabled non-invasive inflammation imaging (in vivo)	[80]
Thyroid Cancer	Gold NPs	Folate, RGD peptides	SERS, CT, MRI	PTT, radiosensitization	Enhanced imaging contrast; tumor regression and radiosensitization in mouse models	[32]
Thyroid Cancer	Iron Oxide NPs	Passive	MRI	Magnetic hyperthermia	Tumor volume reduction; inhibited metastasis in vivo	[61]
Thyroid Cancer	Au-Fe3O4 Composite	Dual targeting ligands	Multimodal (US + MRI + CT)	Combined PTT + hyperthermia	Synergistic imaging and therapy with enhanced survival in mice	[81]

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Table 2 Overview of Clinical Progress of Metallic Nanoparticles in Thyroid Disease Applications

Disease	**NP Type**	**Stage**	**Model/System**	**Key Findings**	**Reference**
Benign Nodules	Gold NPs	Preclinical	Rodent ex vivo	Enhanced US contrast, improved diagnostics	[82]
Benign Nodules	Iron Oxide NPs	Preclinical	Rodent in vivo	Effective magnetic hyperthermia nodule ablation	[83]
Hyperthyroidism	Gold NPs	Preclinical	Rat model in vivo	Significant hormone level reduction post-PTT	[13]
Hyperthyroidism	Iron Oxide NPs	Preclinical	Rodent in vivo	Safe and effective magnetic ablation	[84]
Hypothyroidism	Drug-loaded AuNPs	Preclinical	Rodent oral delivery	Sustained hormone release, improved bioavailability	[13]
Thyroid Cancer	Gold NPs	Early Human	Pilot clinical trial	Enhanced imaging and radiosensitization; safe profile	[85]
Thyroid Cancer	Iron Oxide NPs	Preclinical	Murine tumor model	MRI contrast and tumor ablation	[86]
Thyroid Cancer	Composite Au-Fe3O4 NPs	Preclinical	Murine model	Multimodal theranostics; improved survival	[24]

Table 3 Comparative Overview of AuNPs and IONPs Nanoparticles, Highlighting Their Physicochemical Properties

Parameters	**AuNPs**	**IONPs**
Physicochemical Characteristics	Strong localized surface plasmon resonance (LSPR), tunable size and shape (10–100 nm), easy surface modification, good stability[87]	Superparamagnetic behaviour (Fe_3O_4), strong MRI contrast, magnetic hyperthermia capability, core size ~5–30 nm[88]
Functionalization Strategies	Antibodies, peptides, DNA for organ/tumor targeting.[87]	Ligands for receptor targeting, PEG/biopolymer coatings, magnetically guided accumulation[89]
Imaging Modality	Optical imaging, photoacoustic, CT contrast, plasmon-enhanced imaging[90]	MRI (T_2/T_1 weighted), Magnetic Particle Imaging (MPI), sometimes US/SPECT fusion[89]
Therapeutic Modality	Photothermal therapy (PTT), drug delivery, and radiosensitization[90]	Magnetic hyperthermia (MH), targeted drug delivery, magnetically-mediated ablation[89]
Clinical Advantages	High imaging contrast; combined therapy and theranostics; tunable surface chemistry[90]	Excellent MRI contrast; non-ionizing imaging; magnetic therapy feasible; promising theranostic potential.
Clinical Disadvantages	Potential accumulation in liver/spleen; biodistribution and clearance concerns; clinical translation slow[91]	Precision of hyperthermia challenging; biodistribution/ toxicity concerns; organ clearance issues[92]

Clinical research on metallic nanoparticles for thyroid diseases is still in its early stages, with most studies limited to Phase I trials focused primarily on thyroid cancer. Some of these emerging efforts, including those investigating carbon-based nanoparticle systems, are summarized in Table 4.

Despite promising preclinical data on metallic nanoparticles in thyroid oncology, clinical translation remains limited. Current trials, as outlined in Table 3, are restricted to Phase I studies employing carbon-based nanoparticles for lymphatic mapping and surgical guidance in papillary thyroid carcinoma. While these platforms offer biocompatibility and procedural utility, they lack the multifunctional theranostic capabilities of metallic systems such as gold and iron oxide nanoparticles. The absence of metallic nanoparticle-based trials reflects unresolved challenges related to toxicity, biodistribution, and regulatory compliance. Systematic data on biodistribution and endocrine safety in benign thyroid disorders remain limited. Regulatory bodies, including the U.S. Food and Drug Administration (FDA) and the European

Table 4 Ongoing and Completed Clinical Trials Involving Metallic Nanoparticles in Thyroid Cancer

Disease Type	NP Type	Trial ID (Phase)	Status	Intervention Details
Thyroid Cancer	Carbon Nanoparticle-Loaded Iron (CNSI-Fe(II))	NCT06048367 (Phase I)	Recruiting	Intratumoral injection; assessing safety, tolerability, pharmacokinetics, and preliminary efficacy in advanced solid tumors, including thyroid cancer.
Thyroid Cancer	Carbon Nanoparticle-Loaded Iron [CNSI-Fe(II)]	NCT02724176 (Phase I)	Completed	Evaluating the benefits of carbon nanoparticle injection timing in patients with papillary thyroid cancer.
Thyroid Cancer	Carbon Nanoparticles (CNSI)	NCT04312087 (Phase I)	Active, not recruiting	Using carbon nanoparticles for lateral neck lymph node mapping in patients with papillary thyroid carcinoma.

Note: Data Retrieved From https://clinicaltrials.gov/ (Accessed in July 2025).

Medicines Agency (EMA), continue to evaluate metallic nanoplatforms under combination-product frameworks, highlighting the absence of standardized testing protocols for nanoparticle clearance, immunogenicity, and thyroid-specific long-term safety.[93,94] Advancing these platforms into clinical settings requires rigorous standardization and integration into disease-specific therapeutic frameworks, particularly for aggressive thyroid malignancies.

Theranostic Potential and Translational Barriers

Nanoparticle-Driven Improvements

The integration of metallic nanoparticles (NPs) into thyroid disease management offers several compelling advantages.[13,95] Primarily, these nanoplatforms enable multimodal diagnosis and therapy within a single system, allowing for simultaneous imaging, targeted drug delivery, and therapeutic intervention (Figure 6). For example, gold and iron oxide nanoparticles have been effectively utilized for combined photoacoustic imaging and photothermal

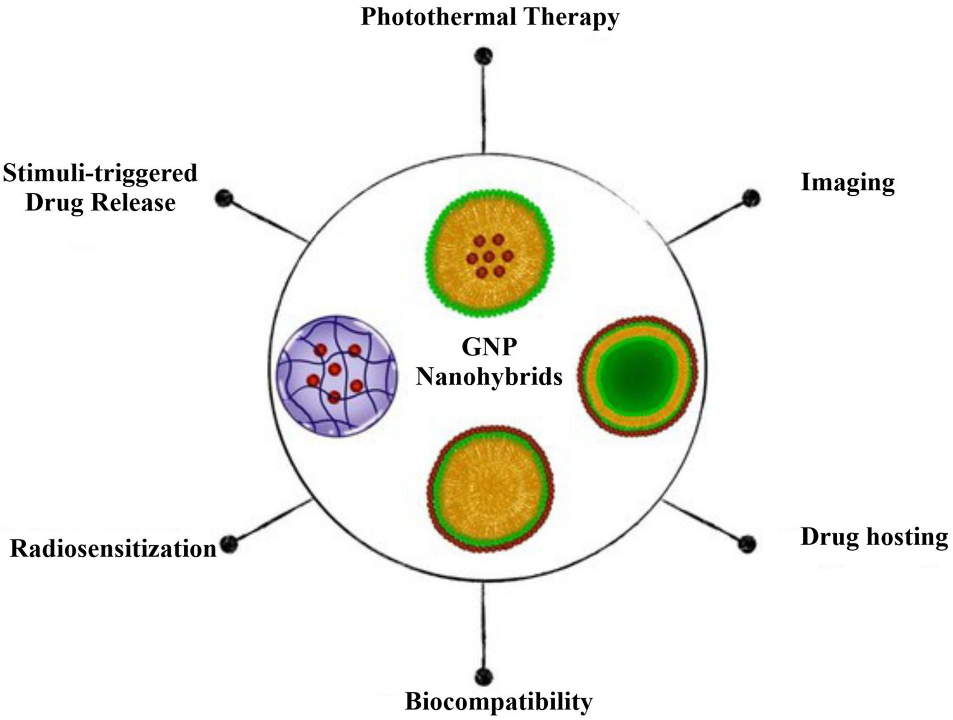

Figure 6 Schematic representation of the multifunctional advantages offered by gold nanoparticle (GNP) nanohybrids in theranostics. These platforms enable simultaneous imaging, targeted drug delivery, and therapeutic intervention within a single nanostructure. Specifically, in thyroid disease management, GNP-based hybrids have been effectively employed for photoacoustic imaging and photothermal therapy, enabling precise tumor localization and ablation. Functionalization with disease-specific ligands enhances targeted accumulation and reduces off-target toxicity. Adapted from the reference[100] under the terms and conditions of a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

therapy, which facilitates precise localization and ablation of pathological tissue. Such multifunctionality not only improves diagnostic accuracy but also enhances therapeutic efficacy.[96] Further, the enhanced targeting capabilities of metallic NPs significantly reduce systemic side effects commonly associated with conventional therapies. By functionalizing nanoparticles with disease-specific ligands, accumulation at the pathological site is maximized, sparing healthy thyroid and surrounding tissues.[97] This specificity is crucial across the disease spectrum from benign nodules and hyperthyroidism to malignant thyroid cancers, resulting in improved patient outcomes. Moreover, metallic nanoparticles facilitate real-time monitoring of treatment response through imaging modalities such as MRI and CT, providing clinicians with timely feedback to adjust therapeutic strategies dynamically.[98,99] This capability supports personalized medicine approaches and can shorten treatment cycles by promptly identifying ineffective interventions.

Translational Barriers

While metallic nanoparticles (MNPs) hold considerable promise for theranostic applications in thyroid disorders, several unresolved challenges continue to hinder their effective clinical translation. One of the primary limitations lies in the heterogeneity of nanoparticle biodistribution across different thyroid pathologies. Inflammatory conditions such as Hashimoto's thyroiditis exhibit altered immune microenvironments and vascular permeability compared to focal nodules or neoplastic lesions.[101,102] These microenvironmental variations significantly impact nanoparticle localization, internalization, and subsequent therapeutic efficacy. Consequently, a one-size-fits-all approach to nanoparticle design proves inadequate.[103–105] Instead, precision-engineered nanostructures that can dynamically respond to pathological cues such as pH shifts, enzymatic activity, or immune markers are increasingly necessary to ensure disease-specific targeting and functionality. Furthermore, the physicochemical properties of MNPs, including particle size, surface charge, and ligand functionalization, directly influence their systemic behavior and tissue-specific accumulation.[106,107] For example, particles under 20 nm often exhibit enhanced renal clearance but may also penetrate non-target tissues more readily, increasing the risk of off-target effects.[108] In contrast, larger particles accumulate preferentially in reticuloendothelial organs such as the liver and spleen, raising concerns about chronic toxicity and long-term retention.[109] Meta-analyses reported metallic nanoparticle cores persist in spleen and liver for months to years, with measurable deposits leading to oxidative stress, mitochondrial dysfunction, and low-grade inflammation in animal models. Investigations also reveal MNP exposure modulates immune signaling, with upregulation of IL-6, TNF-α and complement activation products even at sub-therapeutic doses, suggesting that immune responses as translational barrier.[110]

Oxidative stress induced by metal-based nanoparticles, particularly through reactive oxygen species (ROS) generation, has been implicated in mitochondrial dysfunction, DNA damage, and pro-inflammatory responses. Addressing these safety concerns necessitates comprehensive in vivo toxicokinetic profiling that includes dose-dependent clearance studies, biodegradability assessments, and immunocompatibility evaluations.[111–113] Recent advances in nanomedicine emphasize the functionalization of metallic nanoparticles with polyethylene glycol (PEG), often via monophosphonic or multiphosphonic acid linkers, to create a stealth-like surface that resists protein corona formation and prolongs systemic circulation.[114] Surface modifications like anti-PEG antibodies may accelerate clearance of PEGylated nanoparticles and evoke hypersensitivity responses, revealing immune clearance and cost of modification as a translational challenge.[115] Multivalent phosphonic-PEG coatings have demonstrated superior stability and robustness in physiological serum, maintaining dispersity over months, compared to monovalent analogs that tend to degrade more rapidly. In thyroid theranostics, such stealth coatings reduce recognition and clearance by the mononuclear phagocyte system, enabling higher tumor-to-normal organ accumulation.[116] Moreover, PEGylated nanoscale metal-organic frameworks (NMOFs) labeled with ^{131}I have shown significantly prolonged retention in thyroid tumors and enhanced therapeutic outcomes in murine models, underscoring their potential in differentiated thyroid carcinoma treatment.[117] Beyond regulatory constraints, the clinical deployment of metallic nanoparticle formulations is further impeded by translational limitations related to manufacturing scalability, process reproducibility, and economic sustainability. Reproducing lab-scale formulations under Good Manufacturing Practice (GMP) conditions requires stringent control over critical quality attributes, including hydrodynamic size, polydispersity index, zeta potential, and surface functionalization density, all of which significantly influence in vivo performance. Batch-to-batch variability, particularly in multi-component platforms integrating targeting ligands or theranostic payloads, remains a formidable challenge. Emerging manufacturing technologies, such as microfluidic-based nanoprecipitation and scalable flash nanoprecipitation systems, have demonstrated promise in enhancing reproducibility while preserving nanoparticle functionality. However, these approaches demand substantial capital investment, rigorous GMP validation, and high-purity input materials, all of which contribute to elevated production costs. Until robust, cost-efficient production platforms are established and validated at clinical scale, the widespread adoption of nanoparticle-based therapies in endocrine oncology and benign thyroid disease will likely remain constrained.[118–120]

Emerging Trends and Strategic Directions

Beyond the promising stimuli-responsive functionalities, the clinical translation of metallic nanoparticles in thyroid theranostics critically depends on their ability to maintain physicochemical integrity during large-scale production and in vivo circulation. A growing body of research has focused on lipid–polymer hybrid nanocarriers incorporating redox-responsive disulfide or diselenide linkers, which remain stable under extracellular oxidative conditions but undergo cleavage within the reductive intracellular environment, enabling site-specific release of therapeutic payloads. These smart platforms facilitate precise drug delivery to thyroid tissues characterized by dysregulated redox homeostasis, a feature often observed in aggressive or inflammatory thyroid microenvironments.[121,122]

Thermosensitive iron oxide-based nanoparticles, often coated with polydopamine or PEGylated polymer matrices, have demonstrated dual-functional capabilities, combining magnetic resonance imaging (MRI) contrast enhancement with localized photothermal therapy (PTT). This multifunctionality not only improves the precision of tumor localization but also enhances therapeutic selectivity through heat-induced cytotoxicity in hypervascular thyroid lesions. However, translating such nanoplatforms into clinical practice necessitates rigorous optimization of key performance parameters, including lower critical solution temperature (LCST), linker density, and thermal or magnetic activation thresholds, which must be reproducibly maintained across Good Manufacturing Practice (GMP)-compliant batches. Moreover, comprehensive preclinical validation encompassing dual-trigger activation studies, biodistribution mapping, renal and hepatic clearance kinetics, and immunological profiling is essential to meet regulatory requirements and ensure clinical safety. Only through such multidimensional design and validation strategies can nanoparticle-based therapies achieve personalized, high-fidelity intervention in the complex landscape of thyroid disease.[120]

Interdisciplinary collaboration between endocrinologists, radiologists, and nanomedicine researchers has emerged as a key enabler of clinical translation. Recent studies in thyroid imaging show that AI-augmented ultrasound and multi-modal radiomics platforms developed by teams of radiologists and computational scientists achieved high sensitivity and specificity in nodule classification of a deep-learning model combining B-mode ultrasound and strain elastography validation for TI-RADS4 nodules.[123] Advanced deep learning architectures, such as convolutional neural networks (CNNs), have been trained to perform automated nodule detection, segmentation, and classification tasks with sensitivity and specificity comparable to expert radiologists.[124,125] For instance, studies applying AI to thyroid ultrasound have demonstrated enhanced sensitivity in identifying malignant nodules, reducing false-negative rates while maintaining specificity at a clinically acceptable level.[126] When combined with nanoparticle-derived imaging agents that amplify contrast or provide functional cues (pH-sensitive or enzyme-responsive probes), AI algorithms can exploit high-dimensional radiomic features as texture, heterogeneity, and contrast kinetics to discriminate lesion subtypes and predict molecular phenotypes, even those not visible to the naked eye.[127] The integration of artificial intelligence (AI) into nanoparticle-enhanced imaging modalities such as ultrasound and magnetic resonance imaging (MRI) represents a paradigm shift in diagnostic precision. State-of-the-art convolutional neural networks (CNNs) have been trained on high-resolution image datasets to autonomously detect and classify thyroid nodules with sensitivity and specificity approaching expert radiologists.[128–130] For instance, contrast-enhanced ultrasound combined with AI-powered segmentation algorithms has significantly improved discrimination between benign and malignant lesions by analyzing perfusion dynamics at a microvascular level. When coupled with nanoparticle contrast agents such as gold-based agents in ultrasound or superparamagnetic iron oxide nanoparticles (SPIONs) in MRI, the resulting platforms generate rich, multifunctional microscale signatures.[131] AI algorithms exploit radiomic features like signal intensity variation, temporal contrast kinetics, and textural heterogeneity to infer underlying histopathological properties capabilities often beyond human visual assessment.[132–134]

Methodology

A systematic literature search was conducted using PubMed, Google Scholar, and Web of Science for articles published between 2015 and 2025. Keywords: combined thyroid disorders (thyroid cancer, hyperthyroidism) with metallic nanoparticles and theranostics. Peer-reviewed original research and reviews were included. ClinicalTrials.gov was searched for ongoing trials. Duplicate and non-peer-reviewed studies were excluded. Data were extracted to provide a comprehensive overview of recent advances, challenges, and prospects in metallic nanoparticle theranostics for thyroid diseases.

Conclusion

This review underscores the significant theranostic potential of metallic nanoparticles across the diverse spectrum of thyroid diseases, ranging from benign nodules and hyperthyroidism to hypothyroidism and thyroid malignancies. The multifunctional capabilities of these nanoplatforms, including enhanced imaging, targeted drug delivery, and localized therapy, offer promising avenues to overcome the limitations of conventional diagnostic and therapeutic approaches. Despite significant preclinical successes and emerging early-phase clinical trials, the translation of metallic nanoparticles into routine clinical practice remains at an incipient stage. Challenges related to biodistribution variability, toxicity concerns, and regulatory complexities necessitate robust, multidisciplinary research efforts to optimize nanoparticle design and ensure patient safety. Given the heterogeneity of thyroid disorders and the distinct requirements for managing benign versus malignant conditions, broad-based nanotheranostic research is urgently needed to develop tailored solutions that address disease-specific pathophysiology. This pursuit demands collaboration across disciplines, integrating expertise in nanotechnology, endocrinology, radiology, and clinical oncology. In conclusion, advancing metallic nanoparticle theranostics for thyroid diseases holds the potential to revolutionize patient care, providing more precise, effective, and personalized interventions. Realizing this promise will require concerted efforts to navigate translational barriers and foster innovative strategies that bridge the gap between laboratory innovation and clinical application.

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The Authors declare that they have no competing financial or non-financial interests or any other interests that might be perceived to influence the results and/or discussion reported in this paper.

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