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Stem Cell Therapy for Hashimoto's Disease - a Promising Treatment Method?

Oliwia Kozyra[1*], Oliwia Bochenek[2], Aleksandra Nowak[3], Jessica Kałuża[4], Adrian Konaszczuk[5], Klaudia Ratyna[6], Mateusz Koper[7], Zofia Szypuła [8], Katarzyna Paluch [9], Małgorzata Skarbek[10]

1. Prague hospital dedicated to the Transfiguration of the Lord Sp. z o. o., Aleja Solidarności 67, 03-401, Warsaw, Poland
2. Grochowski Hospital, Grenadierów 51/59, 04-073 Warsaw, Poland
3. Infant Jesus Clinical Hospital UCC MUW, Lindleya 4, 02-005 Warsaw, Poland
4. University Clinical Centre of the Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland
5. Standalone Public Health Care Facility in Świdnik ul. Leśmiana 4, 21-040 Świdnik Poland
6. Infant Jesus Clinical Hospital UCC MUW, Lindleya 4, 02-005 Warsaw, Poland

7. National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland
8. Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
9. Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
10. Provincial Hospital Center of the Jelenia Gora Valley, Oginskiego 6, 58-506 Jelenia Gora

* Corresponding author
Oliwia Kozyra: kozyraoliwia@gmail.com ORCID: https://orcid.org/0009-0004-4882-3126

Oliwia Bochenek: bochenekoliwia1998@gmail.com; ORCID: https://orcid.org/0009-0005-1482-2544

Aleksandra Nowak: aa.nowak17@gmail.com; ORCID: https://orcid.org/0009-0009-6602-4017

Jessica Kałuża: jkaluza@vp.pl; ORCID: https://orcid.org/0009-0002-5050-2538

Adrian Konaszczuk adrian.konaszczuk.nauka@gmail.com ORICID: https://orcid.org/0009-0006-5775-5035

Klaudia Ratyna: klaudiaratyna@gmail.com ORCID: https://orcid.org/0009-0005-2235-1105

Mateusz Koper: mateusz.koper1998@gmail.com; ORCID: https://orcid.org/0000-0002-1048-2774

Zofia Szypuła: zofia.m.szypula@gmail.com ORCID: https://orcid.org/0009-0007-1671-5587

Katarzyna Paluch: kasia.paluch48@gmail.com ORCID: https://orcid.org/0009-0004-2190-855X

Małgorzata Skarbek skarbek.malgorzata@gmail.com ORCID: https://orcid.org/0000-0001-6227-4283

Abstract

Hashimoto's disease, an autoimmune disorder characterized by chronic inflammation and progressive destruction of the thyroid gland, leads to hypothyroidism and a range of metabolic disturbances. Conventional treatments primarily focus on hormone replacement therapy, which does not address the underlying autoimmune mechanisms. Stem cell therapy has emerged as a potential revolutionary treatment for Hashimoto's disease, aiming to regenerate thyroid tissue and modulate the immune response. This abstract explores the potential of stem cell therapy in restoring thyroid function and reducing autoimmune activity. Preclinical studies using animal models and in vitro human cell studies have demonstrated promising results, showing that stem cells can reduce thyroid inflammation, promote tissue regeneration, and restore hormone production. Early-phase clinical trials are underway to assess the safety and efficacy of mesenchymal stem cells (MSCs) and other stem cell types in patients with Hashimoto's disease. Despite the promise, challenges such as immune rejection, ethical considerations, regulatory hurdles, and cost must be addressed. Ongoing research and technological advancements hold the potential to transform the treatment landscape for Hashimoto's disease, offering hope for improved outcomes and quality of life for patients.

Key words: Hashimoto's disease, stem cells, immune response, mesenchymal stem cells (MSC), MSC transplantation, hematopoietic stem cells (HSCs), immunomodulatory therapies, **regenerative medicine**

Introduction

Hashimoto's disease, an autoimmune disorder affecting the thyroid gland, results in chronic inflammation and eventual hypothyroidism due to the immune system attacking the thyroid tissue [1, 2].The condition involves the destruction of thyroid cells through immune-mediated processes [3]. Hashimoto's thyroiditis is often associated with other autoimmune diseases like anemia, Evans syndrome, and autoimmune hemolytic anemia [4]. The disease is characterized by the presence of antibodies such as TGAb, TPOAb, and TRAb, which contribute to the thyroid cell damage and follicle destruction [5]. Research has shown a potential link between Hashimoto's disease and other conditions like Graves' disease, suggesting a complex interplay within autoimmune thyroid disorders [6]. Additionally, the disease has been associated with cognitive decline in vascular dementia patients, indicating its systemic impact beyond the thyroid gland [7]. Furthermore, studies have highlighted a possible autoimmune connection between periodontitis and Hashimoto's thyroiditis, emphasizing the multifactorial nature of the disease [8]. In exploring treatment avenues, the role of selenium in reducing chronic inflammation in Hashimoto's disease has been investigated, pointing towards potential therapeutic interventions [9]. Stem cell therapy has emerged as a promising approach, with research indicating a surge in stem cells during thyroid regeneration, offering new possibilities for treatment [10, 11]. Understanding the mechanisms of thyroid regeneration and the involvement of stem/progenitor cells is crucial in developing innovative therapies for Hashimoto's disease [12].

1. Overview of Hashimoto's Disease

1.1. Pathophysiology

Hashimoto's disease, also known as Hashimoto's thyroiditis, is an autoimmune condition characterized by the immune system attacking the thyroid gland. This autoimmune response involves the infiltration of the gland by lymphocytes, particularly T-cells, and the production of autoantibodies targeting thyroid-specific proteins like thyroperoxidase (TPO) and thyroglobulin (TG) [13; 14]. Over time, this immune-mediated destruction and apoptosis of the thyroid gland led to chronic inflammation and gradual damage to the thyroid tissue, resulting in hypothyroidism [15, 16]. Research indicates that Hashimoto's disease progresses slowly,

causing chronic thyroid damage [17]. The disease is associated with the presence of lymphocytic infiltration and thyroid-specific autoantibodies [18]. Additionally, Hashimoto's thyroiditis is characterized by the development of antithyroid antibodies that target the thyroid tissue, leading to gradual fibrosis and destruction of thyroid cells [19]. In some cases, Hashimoto's disease can transition to Graves' disease, another autoimmune thyroid condition characterized by hyperthyroidism [20]. However, this shift is rare, highlighting the complexity of autoimmune thyroid disorders and their potential interplay [21]. Moreover, Hashimoto's thyroiditis has been linked to other conditions such as Hashimoto's encephalopathy, where patients may present with confusion and seizures [22]. The disease has also been associated with an increased risk of thyroid cancer [23] and infertility in women [24].

1.2. Symptoms

Hashimoto's disease, an autoimmune thyroid disease leading to hypothyroidism, presents a variety of symptoms that can vary in severity based on the level of hormone deficiency. Common symptoms include fatigue, weight gain, cold intolerance, depression, dry skin and hair, constipation, muscle weakness, joint pain, bradycardia, and goiter [25]. The disease is characterized by the destruction of thyroid tissue due to autoimmune processes, resulting in primary hypothyroidism [26]. Approximately 20% of patients with Hashimoto's disease are initially hypothyroid [27]. Hashimoto's thyroiditis is a chronic autoimmune condition causing systemic inflammation, leading to hypothyroidism and thyroid gland enlargement [28]. Hashimoto's disease has been associated with neuropsychiatric manifestations such as depression, anxiety, and encephalopathy. Patients with Hashimoto's encephalopathy may experience confusion, seizures, and altered consciousness [29]. Additionally, Hashimoto's thyroiditis has been linked to an increased risk of anxiety, depression, and insomnia [30]. Studies have shown a correlation between Hashimoto's disease and higher levels of state anxiety in affected individuals [31]. Moreover, Hashimoto's thyroiditis has been reported to lead to depression, anxiety disorders, and sleep disturbances [32].

1.3. Diagnosis

Diagnosing Hashimoto's disease typically involves a combination of blood tests, ultrasound imaging, and in some cases, fine-needle aspiration biopsy. Blood tests are used to measure thyroid-stimulating hormone (TSH), free thyroxine (FT4), and autoantibodies against thyroid

peroxidase (TPO) and thyroglobulin (TG) [33]. Ultrasound imaging is utilized to assess the size and texture of the thyroid gland, where Hashimoto's disease often presents as diffusely hypoechoic bilateral thyroid parenchyma with heterogeneous echotexture and micronodules [34; 35]. Fine-needle aspiration biopsy may be performed to rule out other thyroid conditions and can aid in the diagnosis of Hashimoto's disease [36]. Autoantibodies play a crucial role in the diagnosis of Hashimoto's disease. Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) are commonly used for diagnosing Hashimoto's thyroiditis [37]. Additionally, the presence of anti-thyroglobulin antibody and anti-thyroid microsomal antibody can be indicative of Hashimoto's thyroiditis [38]. Furthermore, ultrasonographic signs such as micronodulation can be highly diagnostic of Hashimoto thyroiditis, although the features may vary in biopsy-proven masses [39].

2. Current Treatments for Hashimoto's disease

2.1. Thyroid Hormone replacement therapy

Thyroid hormone replacement therapy, commonly utilizing levothyroxine, plays a crucial role in managing Hashimoto's disease by aiming to normalize thyroid hormone levels, alleviate symptoms, and prevent complications [40]. This therapy is typically initiated when serum Thyroid Stimulating Hormone (TSH) levels exceed 10 mU/l [41]. While the primary goal is to restore hormone levels, it is important to note that this treatment does not address the underlying autoimmune process responsible for Hashimoto's disease or halt the progression of glandular destruction [42]. Research suggests that thyroid hormone replacement therapy can have broader effects beyond thyroid function. For instance, it has been associated with improvements in mood [43]. Additionally, studies have shown that hormone replacement therapy can lead to the resolution of arthritis related to Hashimoto's thyroiditis, indicating a potential role of thyroid hormones in the pathogenesis of arthritis [44]. Furthermore, thyroid hormone replacement therapy has been linked to improvements in cognitive functions, particularly in elderly patients with subclinical hypothyroidism, suggesting a positive impact on cognitive impairment [45]. It is essential for thyroid hormone replacement therapy to not only focus on normalizing serum TSH levels but also on achieving the normalization of serum free T4, free T3, and the free T4/free T3 ratio [46]. Moreover, the use of levothyroxine as a monotherapy for thyroid hormone replacement in hypothyroid patients has been widely accepted and proven effective through

serum thyroid function tests [47]. Synthetic thyroxine has largely replaced animal thyroid gland extract as the preferred drug for chronic thyroid hormone replacement [48].

2.2. Immunomodulatory therapies

Immunomodulatory therapies, such as corticosteroids and immunosuppressive drugs, have been investigated for their potential in reducing thyroid inflammation and autoimmunity in conditions like Hashimoto's disease. These promising treatments are not commonly used due to the lack of consistent efficacy and safety data [49]. Corticosteroids, in particular, have been associated with favorable outcomes in conditions like Hashimoto's encephalopathy, with the long-term prognosis being positive with steroid therapy, although additional immunosuppressive therapy may be necessary in some cases [50]. However, it is important to note that despite a strong response to corticosteroid treatment, some patients may exhibit a chronic-relapsing course and require long-term immunosuppression [51]. Studies have highlighted the importance of immunosuppressive therapy in managing autoimmune conditions associated with thyroid dysfunction. For instance, in cases of Hashimoto's encephalopathy, proper treatment with immunosuppressive therapy, such as corticosteroids, has been shown to lead to reversible clinical manifestations [52]. Similarly, in autoimmune endocrinopathies like Hashimoto's thyroiditis, immunosuppressant therapies, particularly corticosteroids, have been effective in managing the condition [53].

2.3. Dietary and Lifestyle Interventions

Dietary and lifestyle modifications, such as a gluten-free diet, selenium supplementation, and stress management, have been proposed to support thyroid health and reduce autoimmune activity. While these interventions can be beneficial for some patients, it is important to note that their effectiveness is not universally validated by robust scientific evidence. Selenium, an essential trace element, plays a crucial role in thyroid hormone synthesis, activation, and metabolism [54]. Studies have suggested that selenium supplementation may lead to a reduction in anti-thyroperoxidase antibody levels and improved thyroid ultrasound features in patients with autoimmune thyroiditis [55]. However, conflicting results exist, as some research indicates that selenium supplementation may not decrease thyroid peroxidase antibody concentrations in children and adolescents with autoimmune thyroiditis [56]. Furthermore, selenium deficiency has been associated with the development of thyroid disorders, and supplementation may

optimize thyroid hormone feedback and decrease stimulation of residual thyroid tissue [57]. While selenium supplementation has shown positive effects in some studies, the clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis lacks sufficient documentation based on systematic reviews and meta-analyses [58]. In addition to selenium, lifestyle interventions, including dietary changes, have been explored in the context of thyroid health. A randomized controlled trial found that a lifestyle (dietary) intervention reduced tiredness in children with subclinical hypothyroidism, suggesting that dietary changes can improve thyroid functioning [59]. Lifestyle interventions tailored to specific populations, such as women with newly diagnosed Hashimoto's thyroiditis in areas with low selenium status, have shown positive effects on thyroid health [60].

3. Stem cell therapy: an overview

3.1. What are stem cells?

Stem cells are undifferentiated cells known for their unique ability to differentiate into various cell types and self-renew. They can be broadly categorized into three main types: embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem cells (iPSCs) [61]. Embryonic stem cells are derived from early-stage embryos and possess the remarkable capacity to differentiate into any cell type in the body [62]. On the other hand, adult stem cells are found in various tissues and have a more limited differentiation potential compared to ESCs, but they play a crucial role in tissue repair and regeneration [63]. Induced pluripotent stem cells are generated by reprogramming adult cells to an embryonic-like state, offering a promising avenue for regenerative medicine [64]. The differentiation potential of stem cells is a key factor in their classification. Pluripotent stem cells, such as ESCs and iPSCs, have the ability to give rise to cells of all three embryonic lineages, while multipotent stem cells, like mesenchymal stem cells (MSCs), can differentiate into multiple specialized cells within a specific lineage [65]. Stem cells are characterized by their properties of self-renewal and differentiation, which are essential for maintaining tissue homeostasis and have significant implications for regenerative medicine and therapeutic applications [66].

3.2. Mechanisms of stem cell therapy

Stem cell therapy is a promising approach for tissue repair and immune modulation through various mechanisms. Stem cells possess regenerative potential, allowing them to differentiate into specific cell types to replace damaged tissues [67]. Additionally, stem cells exhibit immunomodulatory properties by secreting bioactive molecules that can modulate the immune system, thereby reducing inflammation and autoimmunity [68] Moreover, stem cells release growth factors and cytokines that promote tissue repair and regeneration through paracrine effects [69] Research has shown that stem cells play a crucial role in tissue repair by facilitating tissue-specific homing and employing mechanisms such as immunomodulation of the local microenvironment, differentiation into functional cells, paracrine secretion, immunoregulation, and intercellular mitochondrial transfer [70]. Mesenchymal stem cells (MSCs) have been particularly highlighted for their benefits in tissue regeneration and immunomodulation [71]. These cells have been studied for their ability to modulate the immune response through the expression of local factors that influence T-cell regulation and the modulation of cytokine expression [72]. Furthermore, the immunomodulatory properties of stem cells have been linked to their ability to release cytokines and growth factors, which not only aid in immunomodulation but also contribute to angiogenesis and stimulate adjacent cells through paracrine mechanisms [73]. Stem cell therapy, especially using exosomes secreted by stem cells, has shown therapeutic effects in immunomodulation, anti-apoptosis, anti-fibrotic, and angiogenesis processes [74].

3.3. Stem cell therapy for autoimmune diseases

Stem cell therapy has emerged as a promising approach for treating various autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. Mesenchymal stem cells (MSCs) are often utilized in these therapies due to their immunomodulatory properties and their ability to home to sites of inflammation [75]. MSC transplantation has shown efficacy in regulating immune cells and has been identified as a potential therapeutic strategy for autoimmune diseases [76]. Studies have highlighted the immunomodulatory potential of stem cell therapy in managing autoimmune diseases by suppressing immune responses and promoting tissue repair [77]. MSCs have been extensively researched for their immunosuppressive, anti-inflammatory, and regenerative capabilities, making them a promising candidate for cell-based therapies in autoimmune disorders [78].

Additionally, MSCs have been shown to possess immunomodulatory properties that can suppress immune cell functions, offering new avenues for treating autoimmune diseases like rheumatoid arthritis [79]. Furthermore, gingival-derived MSCs have demonstrated immunomodulatory properties that make them a valuable tool for treating autoimmune diseases such as rheumatoid arthritis [80]. These cells have been studied for their ability to suppress the functions of immune cells, suggesting their potential in developing novel therapies for autoimmune conditions [81]. Additionally, MSCs have been investigated for their therapeutic effects in autoimmune diseases like multiple sclerosis, offering hope for effective treatment methods [82].

3.4. Mesenchymal stem cells (MSCs)

Mesenchymal Stem Cells (MSCs) are a crucial population of adult stem cells found in various tissues, including bone marrow and adipose tissue. These cells exhibit remarkable immunomodulatory properties and the ability to differentiate into bone, cartilage, and fat cells [83]. MSCs play a significant role in inhibiting the proliferation and function of immune cells such as T-cells and B-cells, promoting the generation of regulatory T-cells (Tregs) that help suppress autoimmunity, and secreting anti-inflammatory cytokines that aid in reducing inflammation and tissue damage [84]. Research has shown that MSCs possess potent immunosuppressive capabilities and can exert therapeutic effects in various diseases, particularly inflammatory disorders, in both animal models and clinical settings [85]. Additionally, MSCs have been utilized in human clinical trials and veterinary medicine for treating inflammatory and immune-mediated diseases [86]. The immunomodulatory functions of MSCs have been further highlighted in studies demonstrating their ability to modulate the immune system by inhibiting dendritic cell differentiation and maturation, thereby influencing the initial steps of the immune response [87]. Furthermore, MSCs have been investigated for their regenerative potential in liver fibrosis, with studies indicating that these cells can have a regenerative impact when cultured with factors such as melatonin, growth factors, and cytokines [88]. The therapeutic effects of MSCs have also been explored in lung diseases, where they have shown anti-inflammatory effects and efficient regenerative capacity.

3.5. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells (HSCs) are a crucial component of the body's blood cell production system, residing in the bone marrow and blood, with the remarkable ability to differentiate into various blood cell types, including immune cells [89]. The concept of hematopoietic stem cell transplantation (HSCT) has emerged as a groundbreaking approach in the treatment of severe autoimmune diseases by essentially resetting the immune system [90]. This process involves the administration of high-dose immunosuppressive therapy to eliminate the existing immune cells, followed by the infusion of HSCs to regenerate a new immune system that is more tolerant and less prone to autoimmune responses [91]. The use of HSCT has become a standard of care for a wide range of hematologic diseases, both malignant and nonmalignant, highlighting its versatility and effectiveness in clinical practice [92]. Specifically, in the context of autoimmune disorders, HSCT stands out as a curative treatment option for various nonmalignant conditions, including autoimmune diseases, inborn metabolic disorders, hemoglobinopathies, and immunodeficiency disorders [93]. The potential of HSCT in addressing autoimmune conditions was first demonstrated in 1997 when it was reported as a treatment for systemic lupus erythematosus, marking a significant milestone in the field [94]. Moreover, HSCT has shown promise in the treatment of specific autoimmune diseases such as multiple sclerosis, where T cell-depleted autologous HSC transplantation has been explored as a therapeutic strategy [95]. This approach involves the infusion of CD34-positive HSCs to establish a new hematopoietic and immune system, offering a potential avenue for managing autoimmune conditions [96]. Similarly, in diseases like Stiff Person Syndrome, autologous stem cell transplantation has been investigated, showcasing the potential of regenerating a naive immune system through the infusion of autologous HSCs [97]. The application of HSCT extends beyond autoimmune diseases to conditions like septic outcomes in patients undergoing autologous stem cell transplantation, where HSC infusion has been linked to a reduction in chemotherapy-induced myelosuppression and procedure-related mortality rates [98]. Additionally, HSCT has been associated with rare complications such as cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) vasculitis post-transplantation, underscoring the importance of monitoring and managing potential adverse effects in clinical practice [99]. In the realm of autoimmune diseases, autologous hematopoietic stem cell transplantation (AHSCT) has emerged as a significant therapeutic approach for severe and therapy-refractory conditions [100]. This treatment modality has been viewed as an experimental but promising

option for addressing a spectrum of autoimmune diseases, offering new possibilities for patients with challenging conditions [101]. The efficacy of AHSCT has been demonstrated in various studies, with outcomes suggesting its potential as a standard treatment for severe autoimmune diseases [102]. Furthermore, the use of HSCT in systemic sclerosis has shown positive results, with autologous hematopoietic stem cell therapy proving effective in managing the most severe forms of the disease [103]. Similarly, in the context of autoimmune cytopenias, HSCT has been reported as a viable treatment option for conditions like immune thrombocytopenia and autoimmune hemolytic anemia, showcasing its versatility in addressing diverse autoimmune manifestations [104]. Allogeneic hematopoietic stem cell transplantation has also been explored in the correction or improvement of autoimmune disorders, demonstrating its potential in modulating immune responses and disease processes [105]. High-dose cyclophosphamide followed by hematopoietic stem cell transplantation has been investigated as a treatment strategy for severe autoimmune disorders like systemic lupus erythematosus, highlighting the evolving landscape of therapeutic interventions in autoimmune conditions [106].

4. Potential of stem cell therapy for Hashimoto's disease

Stem cell therapy shows potential for the treatment of Hashimoto's disease by addressing key aspects of the condition. Research indicates that stem cell therapy has the potential to restore thyroid function, modulate the immune response, and improve the quality of life for individuals with Hashimoto's disease [107]. Hashimoto's disease is characterized by chronic thyroid damage and autoimmune activity, leading to hypothyroidism over time [108]. The disease involves lymphocytic infiltration of the thyroid, contributing to the destruction of thyroid tissue and hormone production [109]. Studies have suggested that factors such as vitamin D may play a role in modulating the immune response in Hashimoto's disease, potentially reducing autoimmune activity and thyroid damage [110]. Symptoms of Hashimoto's disease, such as weight gain, coldness, and fatigue, are a result of the lack of thyroid hormones, highlighting the importance of restoring thyroid function in treatment [111]. Stem cell therapy offers a potential avenue for regenerating thyroid tissue and restoring hormone production, addressing the root cause of these symptoms [112]. Moreover, the autoimmune nature of Hashimoto's disease emphasizes the importance of modulating the immune response to prevent further destruction of the thyroid gland [113]. Stem cell therapy may provide a way to regulate immune activity and reduce autoimmune responses, potentially slowing down the progression of the disease [114]. By targeting these aspects of Hashimoto's disease, stem cell therapy has

the potential to not only restore thyroid function and modulate the immune response but also improve the quality of life for patients by alleviating symptoms and reducing the need for lifelong hormone replacement therapy [115].

4.1. Mechanisms of action

4.1.1. Regeneration of thyroid tissue

Stem cell therapy holds promise for regenerating thyroid tissue and potentially restoring thyroid function in individuals with thyroid disorders such as hypothyroidism. Researchers are investigating various methods to utilize the differentiation potential of stem cells into thyroid follicular cells responsible for producing thyroid hormones. These differentiated cells can potentially be transplanted into the thyroid gland to aid in tissue regeneration and hormone production [116; 117; 118]. Studies have emphasized the importance of mesenchymal stem cells' secretome in regenerating damaged follicular thyroid tissue following thyroid lobectomy, providing a potential alternative to hormone replacement therapy [119]. Additionally, research on generating thyroid tissues from embryonic stem cells through blastocyst complementation shows promise in supplementing thyroid hormone levels [120]. Successful differentiation of human-induced pluripotent stem cells into functional thyroid follicular cells has been achieved, allowing for the creation of thyroid tissues for regenerative medicine applications. Furthermore, the involvement of stem and progenitor cells in the in vivo regeneration of the thyroid after severe damage has been demonstrated, highlighting the regenerative capacity of these cells in restoring thyroid function [121]. These advancements in stem cell research offer significant potential for developing innovative therapeutic strategies for individuals with thyroid disorders, providing hope for enhanced treatment options beyond conventional approaches.

4.1.2. Immunomodulation

Mesenchymal stem cells (MSCs) play a crucial role in modulating the immune system through various mechanisms. They have been found to reduce the activity of autoreactive T-cells and B-cells attacking the thyroid gland, promote the generation of regulatory T cells (Tregs) that suppress autoimmune responses, and secrete anti-inflammatory cytokines that help reduce inflammation and tissue damage in the thyroid [122; 123]. Recent studies have highlighted that MSCs exert their immunomodulatory functions through the secretion of

extracellular vesicles (EVs), which deliver parent cell cargo to recipient cells without causing oncogenicity or variability [124]. These EVs contain anti-inflammatory compounds that interact with immune effector cells, thereby modulating the immune response [125]. Furthermore, Toll-like receptors (TLRs), especially TLR3 and TLR4, highly expressed on MSCs, can significantly influence the immunosuppressive and anti-inflammatory functions of MSCs when activated [126]. Additionally, the CD73/adenosine pathway has been identified as contributing to the immunosuppressive ability of MSCs in autoimmune responses [127]. MSCs have been investigated for their potential in treating autoimmune diseases due to their immunomodulatory properties. They have been shown to ameliorate β cell damage, inhibit the activation and proliferation of immune cells, and regulate immune responses in autoimmune disorders [128; 129; 130].

4.1.3. Preclinical Studies

4.1.3.1. Animal models

Stem cell therapy has shown promise in preclinical studies using animal models of autoimmune thyroiditis, specifically Hashimoto's disease. These studies have indicated that stem cell transplantation can effectively reduce thyroid inflammation, promote the regeneration of thyroid tissue, and restore hormone production [131]. The utility of animal models in studying autoimmune thyroiditis has been well-established, demonstrating the relevance of these models in advancing our understanding of the disease [132]. In the context of autoimmune thyroiditis, the NOD.H2 h4 mouse model has been particularly valuable in exploring the impact of environmental factors such as iodine on the development of autoimmune thyroiditis [133]. Additionally, the Nod-H2(h4) mouse model has been highlighted as a suitable model for autoimmune lymphocytic thyroiditis, closely resembling human Hashimoto's thyroiditis [134]. Furthermore, studies have utilized animal models to investigate the role of iodine in inducing thyroid autoimmunity, emphasizing the significance of animal models in elucidating disease mechanisms [135]. Moreover, experimental autoimmune thyroiditis models in mice have been instrumental in studying the effects of interventions such as green tea polyphenols and emodin on autoimmune thyroiditis, providing insights into potential therapeutic strategies [136; 137]. These studies underscore the importance of animal models in evaluating novel treatments for autoimmune thyroid diseases.

4.1.3.2. In Vitro Studies

In vitro studies utilizing human thyroid cells and immune cells have provided valuable insights into the mechanisms underlying stem cell therapy for autoimmune thyroiditis, particularly Hashimoto's disease. These studies have revealed that mesenchymal stem cells (MSCs) possess the ability to inhibit the proliferation and function of autoreactive immune cells, facilitate the generation of regulatory T cells (Tregs), and enhance the survival and function of thyroid cells [138; 139; 140; 141]. The interaction between transplanted bone marrow-derived MSCs and regulatory T cells has been investigated in the context of autoimmune conditions such as colitis, demonstrating the immunomodulatory effects of MSCs through the induction of Tregs both in vitro and in vivo [142]. Similarly, studies have highlighted the role of MSCs in generating a CD4+CD25+Foxp3+ Treg cell population during the differentiation process of Th1 and Th17 cells, emphasizing the immunoregulatory potential of MSCs [143]. Furthermore, the regulatory effects of MSCs on the balance between Th17 and Treg cells have been explored, with MSCs shown to modulate the differentiation and functions of these T cell subsets through factors such as hepatocyte growth factor [144]. Additionally, the secretion of exosomal sphingosine 1-phosphate by MSCs has been implicated in regulating the Treg/Th17 balance, further underscoring the immunomodulatory properties of MSCs [145]. Moreover, studies have investigated the impact of MSCs on immune cell populations in various disease contexts, including systemic lupus erythematosus (SLE) and aplastic anemia, highlighting the potential of MSCs to increase Tregs and control disease activity through mechanisms such as indoleamine 2,3-dioxygenase (IDO) induction. These findings suggest that MSCs play a crucial role in modulating immune responses and promoting immune tolerance in autoimmune disorders [146].

4.1.3.3. Clinical trials

Clinical trials are pivotal in establishing the safety and efficacy of stem cell therapy for various diseases, including Hashimoto's disease. While preclinical studies lay the groundwork, clinical trials are essential to confirm the therapeutic potential of stem cells in human subjects [147]. Presently, there are numerous early-phase clinical trials underway investigating the utilization of Mesenchymal Stem Cells (MSCs) and other stem cell types in patients with Hashimoto's disease [148]. The utilization of MSCs in clinical trials is extensive, with over 1050 registered trials exploring their applications in various medical conditions such as

neurodegenerative disorders, cardiac diseases, and autoimmune conditions like Hashimoto's disease [149]. Specifically, in liver diseases, more than 80 clinical trials have focused on the use of MSCs, demonstrating the wide array of diseases being targeted through stem cell therapy [150] Clinical trials involving MSCs have also been prevalent in liver diseases and inflammatory bowel diseases, with over 680 trials registered for cell therapy in these areas [151]. These trials aim to assess the effectiveness of MSCs in treating these conditions and contribute to the growing body of evidence supporting the use of stem cells in regenerative medicine. The escalating number of clinical trials incorporating MSCs underscores the potential of these cells as therapeutic agents for a broad spectrum of diseases, including autoimmune disorders like psoriasis [152]. The immunomodulatory characteristics of MSCs have been a focal point of many trials, indicating their promise in immune-based diseases [153]. Furthermore, the therapeutic benefits of MSCs have been observed in various conditions, leading to their widespread application in regenerative medicine [154].

4.1.3.3.1.1. Phase I trials

Phase I trials are essential for evaluating the safety and tolerability of stem cell therapy. These trials focus on determining the optimal dosage, route of administration, and potential side effects of stem cell treatments [155]. While safety is the primary focus of Phase I trials, some studies, such as the one proposed by, also aim to collect preliminary data on potential efficacy endpoints to inform the design of future Phase II and III trials [156]. The completion of Phase I trials, as demonstrated in the study by , offers crucial evidence regarding the safety and feasibility of stem cell therapies, paving the way for further phases of clinical trials [157; 158; 159]. Furthermore, the nuances and limitations of designing Phase I/II clinical trials for stem cell therapy, as discussed by, underscore the importance of considering both safety and efficacy endpoints in these early-phase studies [160]. Pilot studies, like those conducted by, have not only shown the safety of specific stem cell therapies but have also guided the design of subsequent Phase II trials to explore clinical efficacy [161]. Similarly, the research by on urinary incontinence treatment with mesenchymal stem cells stresses the necessity of Phase I/II trials to evaluate the safety and potential efficacy of stem cell interventions [162].

4.1.3.3.1.2. Phase II trials

Phase II trials for evaluating the efficacy of stem cell therapy in treating Hashimoto's thyroiditis involve larger groups of patients to assess various outcomes. Stem cell therapy aims to impact thyroid function, autoimmune activity, and patient-reported outcomes in individuals with Hashimoto's thyroiditis. Hashimoto's thyroiditis is characterized by autoimmune-mediated destruction of thyroid cells, leading to primary hypothyroidism [163]. The disease involves immune cells causing impairment, destruction of thyroid hormone-producing cells, and tissue fibrosis [164]. Additionally, Hashimoto's thyroiditis is frequently associated with other autoimmune diseases, emphasizing the need for effective treatment strategies [165]. Research suggests that interfering with the leptin signaling pathway could be a novel approach to treating and ameliorating Hashimoto's thyroiditis [166]. Furthermore, autologous stem cell products have shown promise in eliminating pathological cells, potentially offering a lifeline for patients resistant to conventional therapies, aiming to restore a healthy immune system and achieve long-term remission [167]. The pathogenesis, diagnosis, and management of Hashimoto's thyroiditis have been extensively discussed in the literature, highlighting the importance of refining treatment protocols and elucidating underlying mechanisms to enhance patient care and outcomes in autoimmune disease management [168 169]. Stem cell transplantation has been explored as a potential treatment for severe autoimmune diseases, showing promising results in experimental models [170].

4.1.3.3.1.3. Phase III trials

Phase III trials are pivotal in evaluating the efficacy and safety of stem cell therapy in diverse patient populations. These trials are crucial for comparing stem cell therapy with standard treatments to provide definitive evidence for regulatory approval [171]. Determining the appropriate dosage for advancing into Phase III trials is a critical and challenging task during drug development [172]. Successful Phase III trials can lead to the approval of new biologic therapies for regenerative medicine [173]. In the context of cardiovascular diseases, several Phase III trials focus on myocardial ischemia and involve the infusion or injection of autologous bone marrow-derived stem cells [174] These trials aim to robustly address the clinical efficacy of stem cell therapy for myocardial repair [175]. Additionally, the use of stem cell therapy in combination with coronary artery bypass grafting has shown promise in improving left

ventricular function, as evidenced by the PERFECT Phase III trial [176]. Furthermore, recent Phase III randomized studies have demonstrated that autologous hematopoietic stem cell transplantation induces long-term disease remission in autoimmune diseases, showcasing superior efficacy compared to conventional treatments [177]. It is essential to emphasize clear and significant clinical benefits in Phase II studies, as the heterogeneity of human diseases in larger Phase III or IV studies can diminish the significance of minor benefits observed in early trials [178].

5. Challenges and considerations of stem cell therapy

Stem cell therapy, while holding great promise for various medical conditions, comes with inherent risks that need to be carefully managed. These risks include immune rejection, tumorigenesis, and infection. Immune rejection occurs when the body's immune system identifies transplanted stem cells as foreign entities, leading to an immune response against them [179]. Tumorigenesis is another concern, where stem cells have the potential to form tumors or contribute to the development of cancer [180]. Additionally, there is a risk of infection associated with the procedures involved in cell transplantation [181]. To address these risks, it is crucial to evaluate various factors before the clinical use of stem cell-based products. These factors include the type of stem cells, their differentiation status, proliferation capacity, route of administration, intended location, in vitro culture, manipulation steps, irreversibility of treatment, and long-term survival of engrafted cells [182]. Understanding the risk profile associated with stem cell therapies is essential for ensuring their safety and efficacy. In the context of immune rejection, different modes of stem cell-based therapies have been explored, such as autologous transplantation, allogeneic transplantation without human leukocyte antigen-matching, and allogeneic transplantation with matching [183]. Strategies to overcome immune rejection include stem cell-dose escalation and the induction of immunological tolerance before treatment with allogeneic stem cell therapies [184; 185]. Moreover, ethical considerations are paramount in stem cell therapy, especially concerning the use of human embryonic stem cells (hESCs). The destruction of human embryos in hESC research raises significant ethical dilemmas that have limited the development of hESC-based clinical therapies [186]. Allogeneic immune rejection of hESC-derived cells remains a key challenge for the clinical application of hESC-based therapy [187].

5.1. Safety

Stem cell therapy, while holding great promise for treating various diseases, comes with inherent risks that need to be carefully managed. Three significant risks associated with stem cell therapy include immune rejection, tumorigenesis, and infection [188]. The body's immune system may identify transplanted stem cells as foreign entities, leading to an immune response against them [189]. Moreover, there is a concern regarding the potential of stem cells to form tumors or contribute to cancer development [190]. Additionally, the risk of infection is associated with cell transplantation procedures, highlighting the importance of ensuring the safety of the entire process [191]. To address these risks, it is crucial to thoroughly assess the safety of stem cell therapeutics at every stage of development, from the selection of cell sources to preclinical evaluation and eventual transplantation [192]. Understanding the biological mechanisms of stem cell therapy, including the distinction between cellular effects and paracrine effects, is essential for ensuring both efficacy and safety in therapeutic development [193]. Furthermore, the availability of stem cell sources, the challenge of immune rejection from nonautologous sources, and the need for alternative immunosuppression methods are critical considerations in stem cell transplantation therapy [194; 195]. Efforts to mitigate these risks include exploring different modes of stem cell-based therapies, such as autologous transplantation and allogeneic transplantation with or without human leukocyte antigen-matching ([196]. Research also focuses on generating 'universal donor' stem cell lines and inducing immunological tolerance before allogeneic stem cell therapy to address immune rejection concerns [197]. Moreover, advancements in cell replacement therapy using induced pluripotent stem cells are bringing stem cell-based treatments closer to reality for various conditions, including Parkinson's disease.

5.2. Ethical considerations

The use of stem cells in research and therapy presents a complex landscape of ethical considerations. Human embryonic stem cells (hESCs) have been at the center of ethical debates due to the destruction of embryos [198]. In contrast, induced pluripotent stem cells (iPSCs) offer a promising alternative that avoids these ethical dilemmas [199]. iPSCs can be generated from somatic cells without the need to destroy embryos, addressing concerns related to the moral status of human embryos [200]. While iPSCs provide a valuable avenue for research and therapy, their use also necessitates careful ethical considerations. iPSCs have been proposed as

a more ethical option compared to hESCs, which are entangled in significant ethical controversies [201]. The ethical considerations surrounding iPSCs mirror those associated with hESCs, particularly concerning the potential to induce the formation of gametes and the implications for cloning individuals in the future [202]. Moreover, the generation of iPSCs from adult somatic cells offers a way to circumvent ethical concerns associated with embryonic stem cells [203]. iPSCs have the potential to address issues of immunological rejection after cellular transplantation, further highlighting their ethical advantages over hESCs [204].

5.3. Regulatory challenges

Stem cell therapies offer promising treatments for various diseases and conditions in medicine. However, ensuring the safety, efficacy, and quality of these therapies requires rigorous regulatory scrutiny. Regulatory agencies like the FDA mandate comprehensive preclinical and clinical data to approve new stem cell treatments [205]. Clinical trials are essential for advancing stem cell therapies, exploring applications in immune system diseases, hematologic diseases, gastrointestinal diseases, heart diseases, and neurodegenerative diseases [206]. Stem cell therapy has shown potential in conditions like myocardial infarction, aiming to replenish cell loss and induce angiogenesis or activate resident cardiac stem cells [207]. Additionally, stem cell-based therapies have been utilized to repair damaged tissues in organs, showcasing their regenerative potential [208]. Ethical considerations are crucial in stem cell transplantation. Regulations focus on the use and production of embryonic stem cells, adult stem cells, and the patenting of stem cell lines and products [209]. The commercialization of stem cell research presents challenges, with the need to develop therapies quickly while ensuring safety and efficacy [210]. Moreover, the quality of stem cells used in therapy can significantly impact treatment effectiveness [211]. In terms of regulatory responses, there is a growing concern about direct-to-consumer stem cell marketing, emphasizing the need for stringent enforcement activities to protect patients and healthcare markets [212]. Countries like China stress the importance of well-designed clinical trials and robust clinical evidence to secure marketing authorization for stem cell-based products [213].

5.4. Cost and accessibility

Stem cell therapies offer promise for treating various medical conditions, but their high cost and limited accessibility present significant challenges to ensuring equitable access to these

advanced treatments. Despite advancements in stem cell research and therapy, disparities in access persist [214]. The issue of accessibility is particularly crucial in countries with insufficient healthcare infrastructure, where investments in stem cell research are being made [215]. Efforts to address disparities in access to stem cell treatments are essential to improve patient outcomes and promote fairness in healthcare delivery. In the context of healthcare technologies, programs like the Advanced Medical Care Program (AMCP) in Japan aim to facilitate the rapid integration of innovative treatments into national healthcare systems [216]. Such initiatives play a vital role in enhancing access to cutting-edge medical interventions. Additionally, the use of blockchain technology in healthcare systems is gaining traction due to its potential to improve data security and privacy, which could contribute to more efficient and accessible healthcare services [217]. Ensuring equitable access to stem cell therapies aligns with broader efforts to address disparities in healthcare access globally. In the case of hepatitis C treatment, prioritizing access to Direct-Acting Antiviral (DAA) therapies is crucial for reducing the burden of the disease across different income settings [218; 219]. Similarly, initiatives to improve access to medication for conditions like cystic fibrosis and kidney cancer underscore the importance of streamlining processes to enhance patient access to essential treatments [220; 221].

6. Future Directions stem cell therapy for Hashimoto's disease

Stem cell therapy shows promise for the future management of Hashimoto's disease, an autoimmune condition affecting the thyroid gland [222]. Key areas of focus include enhancing stem cell delivery, combination therapies, personalized medicines and Long-Term Follow-Up Studies.

6.1. Enhancing stem cell delivery

Efficient methods for delivering stem cells to the thyroid gland are crucial for enhancing the effectiveness and safety of stem cell therapy. Targeted delivery systems and minimally invasive procedures can significantly improve the precision of stem cell delivery to the thyroid gland. Innovations in biomaterials and nanotechnology offer promising avenues for achieving this precise delivery [223]. Research has shown that stem cells play a vital role in thyroid regeneration. Studies have indicated the presence of resident stem cells or progenitor cells within the thyroid gland that have the capacity to repair and regenerate damaged thyroid tissue

[224]. Understanding the mechanisms of thyroid regeneration and the involvement of stem cells in this process is essential for gaining insights into thyroid diseases and potentially developing new therapeutic approaches [225].Moreover, advancements in generating thyroid follicular cells from various stem cell sources, including embryonic stem cells and induced pluripotent stem cells, have been reported. These studies highlight the potential for differentiating stem cells into hormone-producing thyroid follicular cells in vitro, which could be instrumental in developing cell-based therapies for thyroid disorders [226].Furthermore, the identification of stem/progenitor cells within the thyroid gland and their role in thyroid development and diseases has been a subject of intense research. Studies have suggested that solid cell nests in the thyroid may harbor stem cell properties, indicating their potential involvement in thyroid homeostasis and regeneration [227].

6.2. **Combination therapies**

Combining stem cell therapy with immunomodulatory drugs or gene therapy holds promise for enhancing the therapeutic effects of Hashimoto's disease by addressing multiple aspects simultaneously. Research suggests that utilizing stem cells in conjunction with agents promoting Treg development or inhibiting specific inflammatory pathways could lead to synergistic benefits [228]. This approach aligns with the concept of combining effective stem cell strategies with immunomodulatory drug regimens to improve clinical outcomes [229]. Furthermore, the use of therapeutic gene transfected stem cell therapy may offer a synergistic effect by combining gene therapy and stem cell therapy advantages [230]. By amplifying the endogenous stem cell growth factor network, a combined stem cell and gene therapy approach could potentially enhance therapeutic efficacy [231].

6.3. **Personalized medicine**

Advancements in personalized medicine utilize genomics to customize stem cell therapies for individual patients, optimizing treatment outcomes and reducing adverse effects by moving away from generic treatment approaches [232]. Personalized medicine in stem cell therapy is essential due to the variability among patient factors and the biology of different stem cell types, highlighting the necessity for tailored approaches in cell-based treatments [233] .Stem cells play a crucial role in personalized medicine, offering the potential for regenerative and curative

therapies for various diseases based on individual genetic and immunological profiles [234]. The use of induced pluripotent stem cells (iPSCs) and human embryonic stem cells (hESCs) provides an unlimited cell source for personalized medicine applications, particularly in cell replacement therapy [235]. Replicating stem cell niches is vital for expanding stem cell numbers to realize the promises of regenerative medicine and gene therapy [236]. Personalized or precision medicine integrates genetic information with phenotypic and environmental characteristics to deliver healthcare tailored to the individual, eliminating the constraints of "one-size-fits-all" therapy. The necessity for personalized medicine approaches to stem cell therapy is evident based on these premises.

6.4. Long-term follow-up studies

Long-term follow-up studies are crucial to evaluate the lasting benefits and potential risks of stem cell therapy for Hashimoto's disease. These studies should involve larger sample sizes and extended follow-up periods to comprehensively assess the safety and efficacy of this treatment [237]. Notably, stem cell therapy has shown effectiveness in reducing complications like femoral head collapse over prolonged follow-up periods, highlighting the importance of continuous monitoring for such outcomes [238]. Additionally, studies have emphasized the need for identifying optimal stem cell types for treating radiation-induced tissue injuries through long-term follow-up investigations [239]. Overall, rigorous long-term follow-up studies are essential to ensure the safety and efficacy of stem cell therapy for Hashimoto's disease.

Discussion

Stem cell therapy for Hashimoto's thyroiditis is a topic of debate within the medical community. Proponents of this innovative approach highlight its potential to target the root cause of the disease, which involves the slow destruction of the thyroid gland by B and T cells [240]. However, opponents raise concerns about the premature adoption of this therapy due to the lack of robust clinical evidence, high costs, and ethical considerations [241]. Hashimoto's thyroiditis is characterized by autoimmune processes leading to thyroid tissue destruction, involving cell and antibody-mediated immune mechanisms [242]. The disease presents with distinct histopathological features such as lymphoplasmacytic infiltration, germinal center

formation, follicular destruction, Hurthle cell changes, and varying degrees of fibrosis [243]. Research has shown that Hashimoto's thyroiditis can be subclassified based on immunostaining of IgG4 into IgG4 thyroiditis and non-IgG4 thyroiditis [244]. Additionally, studies have indicated the presence of MHC class II molecules on thyroid follicular cells in patients with Hashimoto's thyroiditis, distinguishing them from normal subjects [245]. Furthermore, the autoimmune nature of Hashimoto's thyroiditis is evident in the presence of antibodies like anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin (TGAb) [246].

Conclusion

As a novel treatment for Hashimoto's disease, stem cell therapy has considerable promise because it can both control the immune system and restore damaged thyroid tissue. Positive preclinical and early-phase clinical trial outcomes imply that stem cell treatment can lessen autoimmune activity and enhance thyroid function. Before stem cell therapy is widely used to treat Hashimoto's disease, a number of obstacles must be overcome, including safety worries, ethical issues, legal restrictions, and financial constraints. Future developments in science and technology will continue to influence stem cell therapy, offering patients with Hashimoto's disease hope for better prognoses and a higher standard of living.

Author's contribution

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