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THE POTENTIAL ROLE OF METFORMIN IN THE TREATMENT OF HASHIMOTO'S THYROIDITIS: REVIEW

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ABSTRACT

Background: Hashimoto's thyroiditis is one of the most common autoimmune diseases, with a noticeable increase in incidence observed in recent years. Despite its high prevalence, current treatment options remain limited and primarily focus on managing the consequences rather than addressing the underlying causes of the condition. Metformin, although primarily prescribed for diabetes, has demonstrated promising anti-inflammatory and immunoregulatory properties in several autoimmune disease models.
Aim: This review aims to evaluate the potential role of metformin in the management of Hashimoto's thyroiditis, with a particular focus on its effects on immune regulation and thyroid function.
Methods: An electronic literature search was performed using PubMed, Cochrane Library, ScienceDirect and Evidence-Based Medicine Reviews. Search terms included 'Metformin', 'Hashimoto disease', 'Thyroiditis', 'Thyroid', 'autoimmune disease' as keywords. Only articles in English were considered.
Conclusions: Preliminary data suggest that metformin, through its anti-inflammatory properties and modulation of AMPK/mTOR pathways, may influence immune responses in Hashimoto's thyroiditis. Despite promising preclinical findings, further clinical trials involving human participants are required to evaluate its therapeutic efficacy and safety in this context.

KEYWORDS

Metformin, Hashimoto Disease, Thyroiditis, Thyroid, Autoimmune Disease

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1.Introduction

Hashimoto's disease is related to autoimmune thyroid diseases (Bellan et al., 2020). In recent years, there has been an increase in the number of cases, with an incidence is 0.3-1.5 cases per 1000 people. (Ragusa et al., 2019; Ralli et al., 2020). The disease affects women approximately 5-10 times more often than men (Klubo-Gwiezdzinska & Wartofsky, 2022; Pyzik et al., 2015). In the pathogenesis of Hashimoto's disease, both cellular and humoral immune responses are involved. The cellular response involves T-helper lymphocytes (Th), regulatory T lymphocytes, and B cells. The humoral response involves specific antibodies against thyroglobulin and thyroid peroxidase (Ajjan & Weetman, 2015; Jin et al., 2022; Wrońska et al., 2024). The etiology is multifactorial, including genetic predisposition and environmental exposures, immunological factors (Cogni & Chiovato, 2013). Genetic factors influencing the disease include histocompatibility genes - human leukocyte antigen (HLA), immune-regulatory genes, e.g, cytotoxic T-lymphocyte associated protein 4 (CTLA4), protein tyrosine phosphatase, non-receptor type 22 (PTPN22), thyroid-specific genes (Hwangbo & Park, 2018; Mikulska et al., 2022; Weetman, 2021). Environmental factors include increased iodine and selenium intake, reduced vitamin D levels, and infections such as hepatitis C, stress (Ajjan & Weetman, 2015; Jin et al., 2022; Santos et al., 2019).

The first historical reference to metformin dates back to 1922, when it was synthesized by Werner and Bell (Bailey, 2017; Werner & Bell, 1922). However, it remained largely overlooked for over two decades, until Eusebio Garcia, in 1949, explored its potential in treating influenza. During that time, metformin was found to reduce blood glucose levels in patients, which drew attention to its possible antidiabetic properties (Bailey, 2017; *Flumamine, a New Synthetic Analgesic and Anti-Flu Drug - PubMed*, n.d.). In 1957, Jean Sterne published a report on the use of metformin for the treatment of diabetes, which led to its introduction in the United Kingdom and other European countries in 1958 (Bailey, 2017; [Treatment of Diabetes Mellitus with N, N-Dimethylguanylguanidine (LA. 6023, Glucophage)] - PubMed, n.d.). Although clinical findings from Europe supported metformin's therapeutic efficacy, the drug was not approved by the U.S. Food and Drug

Administration (FDA) until 1994 due to concerns over lactic acidosis associated with related biguanides. It was introduced to the American market a year later, in 1995 (Bailey, 2017; DeFronzo & Goodman, 1995).

Currently, metformin has been used in the treatment of type 2 diabetes for over 70 years. Interestingly, beyond its metabolic impact, metformin has shown promising effects in mitigating oxidative damage, tissue fibrosis, and abnormal cell growth, as well as in protecting cardiac and renal function (Ursini et al., 2018). Moreover, some recent studies have suggested that metformin may be associated with a decreased risk of cancer development, a lower incidence of neurodegenerative disorders, and even a possible extension of lifespan (Ahmad & Haque, 2024; Dutta et al., 2023; Kim, 2024). In addition, experimental evidence from both in vivo and in vitro studies indicates that it may influence several immune pathways involved in the pathogenesis of systemic autoimmune disorders. These include the regulation of T cell subsets, modulation of cytokine and autoantibodies production, and changes in inflammatory cell behavior and tissue remodeling (Ursini et al., 2018).

Of particular interest is metformin's anti-inflammatory activity, which may offer therapeutic potential in conditions such as Hashimoto's thyroiditis. This review aims to present an overview of current findings concerning metformin's possible application in the management of autoimmune diseases, with a specific focus on its relevance to Hashimoto's thyroiditis.

2. Mechanism of Action of Metformin.

2.1. Mechanism of Action of Metformin AMPK-dependent.

Metformin's primary antihyperglycemic effect is largely attributed to the activation of AMP-activated protein kinase (AMPK), a key energy sensor involved in maintaining cellular energy balance. By inhibiting complex I of the mitochondrial electron transport chain, metformin decreases ATP production while increasing intracellular levels of AMP and ADP. This shift in the AMP/ATP ratio activates AMPK (Rena et al., 2017).

AMPK activation suppresses hepatic gluconeogenesis through the inhibition of key enzymes involved in glucose production. Additionally, AMPK improves peripheral insulin sensitivity by enhancing glucose uptake in skeletal muscle and promoting lipid oxidation, while inhibiting lipogenesis and protein synthesis. These mechanisms explain the multifaceted metabolic benefits of metformin in type 2 diabetes management (Rena et al., 2017; Ursini et al., 2018).

2.2. AMPK-Independent Mechanisms of Metformin Action.

Beyond AMPK activation, metformin also exerts metabolic and immunological effects through AMPK-independent pathways. One such mechanism involves the inhibition of the mTORC1 pathway via induction of REDD1 and Sestrin2, mediated by activating transcription factor 4 (ATF4), independently of AMPK activation (Sahra et al., 2011). This alternative route underscores metformin's capacity to modulate cellular growth and autophagy, even in conditions where AMPK is not active.

In HER2-positive breast cancer models, metformin has demonstrated efficacy by suppressing mTORC1 signaling and reducing tumor proliferation, independently of AMPK, suggesting relevance in oncology and possibly in autoimmune pathologies characterized by dysregulated cell growth (Chae et al., 2016).

Recent research has further expanded our understanding of AMPK-independent mechanisms. Metformin was shown to engage lysosomal pathways through its interaction with presenilin enhancer 2 (PEN2), inhibiting v-ATPase activity and thereby triggering lysosomal signaling events without altering AMP/ATP ratios (Sugawara & Ogawa, 2023). Another line of evidence indicates that metformin reduces mitochondrial reactive oxygen species (ROS), contributing to improved redox balance and inflammatory control independent of AMPK (Vezzaet al., 2023). Additionally, studies have confirmed that metformin can directly modulate autophagy and cell proliferation by targeting mTORC1 even in the absence of AMPK activation, highlighting a broader relevance of these effects in immune and tumor-related pathways (Zamanian et al., 2024).

2.3. Immunometabolic Implications of AMPK Activation by Metformin.

Recent evidence suggests that the downstream consequences of AMPK activation also play a significant role in modulating immune responses. Immune cell function is closely tied to metabolic programming. Pro-inflammatory immune subsets—such as neutrophils, M1 macrophages, and effector T cells—primarily rely on glycolysis for ATP production. In contrast, anti-inflammatory cells like regulatory T cells (Tregs), memory T cells, and M2 macrophages favor mitochondrial oxidative phosphorylation (Ursini et al., 2018).

In this context, AMPK activation by metformin encourages a shift toward mitochondrial energy metabolism, limiting glycolysis and thereby potentially attenuating the activity of pro-inflammatory immune cells.

AMPK also inhibits the mammalian target of rapamycin (mTOR), a key modulator of cell growth, proliferation, and autophagy. In the immune system, mTOR activity is essential for T cell activation and differentiation. Metformin has been shown to inhibit mTOR signaling via both AMPK-dependent and AMPK-independent mechanisms, thus influencing T cell function and possibly dampening autoimmune activity (Ursini et al., 2018).

2.3.1. Mechanisms of Metformin Action on T Cells.

Metformin modulates T cell responses by targeting key immunometabolic pathways, particularly the AMPK/mTOR axis. In autoimmune settings, pathogenic effector T cells such as Th1 and Th17 rely heavily on glycolytic metabolism, while Tregs utilize oxidative phosphorylation (Grant et al., 2015; Singh et al., 2014; Ursini et al., 2018). By activating AMPK and inhibiting mTOR, metformin shifts T cell metabolism toward oxidative pathways, promoting Treg differentiation and suppressing pro-inflammatory Th1/Th17 subsets (Delgoffe et al., 2009; Noack & Miossec, 2014; Saleiro & Platanias, 2015).

In animal models of autoimmune diseases—including experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), and lupus-prone mice - metformin consistently reduced disease severity, lowered IL-17 and IFN-γ levels, and increased Treg frequency, often through suppression of STAT3 signaling downstream of mTOR (Ursini et al., 2018). Moreover, metformin was able to normalize mitochondrial metabolism in T cells, a hallmark of autoimmune dysregulation (Lai et al., 2012; Yin et al., 2015).

Preliminary human data also support these findings. In SLE and multiple sclerosis patients, metformin reduced Th17/Th1 cell frequency and increased Tregs, correlating with improved clinical outcomes and reduced inflammatory burden (Ursini et al., 2018). Furthermore, in type 2 diabetes and polycystic ovary syndrome, metformin was associated with normalization of T cell subsets, including reduced IL-17 levels and increased thymic output (Dworacki et al., 2015).

2.3.2. Mechanisms of Metformin Action on B Cells.

Metformin modulates B cell responses by interfering with their differentiation and function via the AMPK/mTOR/STAT3 axis. It inhibits the differentiation of naive B cells into antibody-producing plasma cells, thereby reducing autoantibody production—a central feature in autoimmune diseases (S.-Y. Lee et al., 2017; Ursini et al., 2018).

Additionally, metformin interferes with BAFF-mediated B cell survival and proliferation by downregulating the mTOR–Akt and Erk1/2 pathways (Chen et al., 2021). Through AMPK activation, it also modulates mitochondrial metabolism in B cells, contributing to reduced pro-inflammatory antibody responses (Xiao et al., 2022).

These effects may be particularly relevant in diseases like SLE, where aberrant B cell activation and survival drive pathology. By restoring metabolic checkpoints, metformin offers a targeted strategy to limit autoreactive B cell responses (Ursini et al., 2018).

2.3.3. Mechanisms of Metformin Action on Macrophages and Monocytes.

Metformin influences macrophage and monocyte activity primarily via AMPK activation, which impacts their metabolic programming and inflammatory phenotype. Through AMPK-dependent pathways, metformin inhibits STAT3 signaling, thereby reducing monocyte-to-macrophage differentiation and dampening pro-inflammatory responses (Vasamsetti et al., 2015). This action may contribute to the attenuation of atherosclerotic plaque formation and other inflammation-related processes (Ursini et al., 2018).

In macrophages, metformin promotes polarization toward an anti-inflammatory M2 phenotype while suppressing the pro-inflammatory M1 profile, notably reducing IL-1β and TNF-α production and enhancing IL-10 secretion (Jing et al., 2018; Park et al., 2017). This shift is partly mediated by AMPK-SIRT1 signaling and inhibition of ROS generation through complex I of the mitochondrial electron transport chain (Kelly et al., 2015).

Additionally, metformin suppresses NF-κB and MAPK pathways in both macrophages and monocytes, further reducing inflammatory cytokine release (Bułdak et al., 2016). It has also been shown to downregulate macrophage migration inhibitory factor (MIF), a key player in chronic inflammation and autoimmunity (Dandona et al., 2004; Leng et al., 2011).

2.3.4. Mechanisms of Metformin Action on Neutrophils.

Metformin modulates neutrophil function by attenuating their pro-inflammatory activity and interfering with neutrophil extracellular trap (NET) formation. NETs, composed of DNA and cytotoxic enzymes, contribute to tissue damage and autoantigen exposure in autoimmune diseases like SLE (Yang et al., 2016; Yu & Su, 2013). Elevated NETosis is linked to hyperglycemia and insulin resistance, both of which are ameliorated by metformin (Menegazzo et al., 2015; Wong et al., 2015).

By activating AMPK and reducing mitochondrial ROS production, metformin suppresses NET formation in vitro and lowers circulating NET biomarkers in vivo (Menegazzo et al., 2018; Wang et al., 2015). This effect may restore immune homeostasis and reduce autoimmunity-associated vascular and tissue injury.

Additionally, metformin has been shown to normalize elevated neutrophil counts and neutrophil-to-lymphocyte ratios (NLR) in states of metabolic inflammation and hyperandrogenism, suggesting broader systemic anti-inflammatory actions (Eilenberg et al., 2017; Ibáñez et al., 2005). Given the association between high NLR and autoimmune disease activity, these effects of metformin may carry prognostic and therapeutic significance (Forget et al., 2017; Wu et al., 2016).

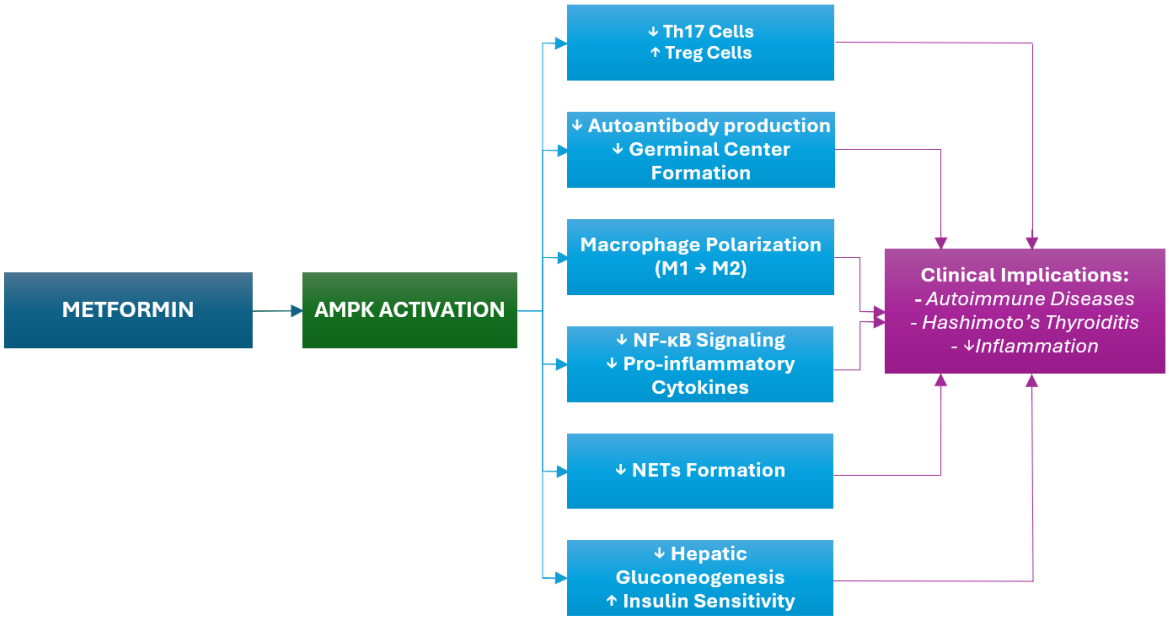

Fig. 1. *Visualization of Simplified AMPK-Dependent Anti-Inflammatory and Immunomodulatory Mechanisms of Metformin.*

3. Clinical and Experimental Insights into the Effects of Metformin in Autoimmune Thyroid Disease.

Krysiak et.al conducted a study involving a group of women who were treated with bromocriptine or cabergoline, with autoimmune thyroid disease and carbohydrate metabolism disorders or diabetes. Additionally, a division into women with subclinical hypothyroidism and high-normal thyrotropin levels subclinical hypothyroidism was used. The changes were more expressed among patients treated with bromocriptine than with cabergoline. This change may be caused by an indirect effect of dopaminergic regulation on thyrotropin function. A decrease in thyrotropin levels was statistically significant and was associated with subclinical hypothyroidism. No changes were observed in free thyroxine, triiodothyronine, anti-TPO, and Tg levels. Changes in the level of thyrotropin after the use of metformin did not correlate with the change in the level of antithyroid antibodies (Krysiak et al., 2015).

A randomized, double-blind, placebo-controlled clinical trial conducted by Severo et. al examined people with subclinical hypothyroidism. Both women and men took part in the study. No statistically significant reduction in TSH was observed (Dornelles Severo et al., 2018).

Research conducted by Jia et al. concerns mice with Hashimoto's disease. They observed a reduction in lymphocyte infiltration and a significant decrease in the level of anti-thyroglobulin antibodies in the group of mice treated with metformin. A significant decrease in the percentage of Th17 lymphocytes and

M1 macrophages was also detected after treatment. Additionally, a reduction in thyroid volume was noted (Jia et al., 2021).

The next study also involved mice. Zhao et al. conducted research examining patients with Hashimoto's disease and mice with spontaneous autoimmune thyroid disease. After metformin treatment, there was a reduction in the extracellular acidification rate and oxygen consumption rate, which were used to assess the metabolism of CD4+ T cells. Moreover, a reduction in the levels of glycolysis-related enzymes in $CD4^+$ T cells was observed, with metformin exerting a specific effect on mTOR expression. Additionally, the use of metformin increased the level of Treg lymphocytes and significantly reduced the Th1 and Th17 ratio, which resulted in reduced thyroid inflammation (Zhao et al., 2021).

4. Discussion.

The etiology of Hashimoto's thyroiditis (HT) is currently considered multifactorial and not yet fully understood. It involves both genetic and environmental factors (H. J. Lee et al., 2015). The pathogenesis of autoimmune thyroid diseases includes the interplay between cellular and humoral immune responses leading to the autodestructive process in the thyroid gland (Ajjan & Weetman, 2015).

Current treatment of Hashimoto's disease is primarily based on levothyroxine replacement therapy, which alleviates the symptoms of hypothyroidism but does not address the underlying causes or prevent progressive thyroid tissue destruction. There is a lack of therapies aimed directly at modulating autoimmune responses, such as inhibiting autoantibody production or the activity of T and B lymphocytes (Ralli et al., 2020; Tywanek et al., 2024).

Given the complex etiology of the disease, potential benefits of metformin treatment have been observed, particularly due to its anti-inflammatory properties.

In a study conducted by Krysiak et al. (Krysiak et al., 2015), the effect of metformin on lowering thyroid-stimulating hormone (TSH) levels was dependent on the concomitant use of dopamine agonists, especially in female patients treated with bromocriptine. This finding suggests a possible role of metformin in regulating the dopaminergic system and its secondary influence on thyroid function (Krysiak et al., 2015; Vigersky et al., 2006). On the hand, a study by Severo et al. (Dornelles Severo et al., 2018) did not demonstrate significant changes in TSH levels. Therefore, it is necessary to conduct a larger number of studies, with a larger number of subjects, covering a longer period of observation (Krysiak et al., 2016).

Neither of these studies (Dornelles Severo et al., 2018; Krysiak et al., 2015) demonstrated a significant effect of metformin on thyroid autoantibody levels, casting doubt on its influence on immunomodulatory mechanisms in Hashimoto's disease. However, in the animal model studies we cited (Jia et al., 2021; Zhao et al., 2021), metformin was found to affect T lymphocyte profiles. Both studies reported changes in Th17 cell levels, as well as in Treg and Th1 lymphocytes and macrophages. These findings suggest a potential immunomodulatory role of metformin.

In a study by L. Zhao et al. (Zhao et al., 2021), metformin significantly inhibited the mTOR pathway, which regulates glycolysis activation in $CD4^+$ T cells. As a result, cellular metabolism shifts from glycolysis toward oxidative phosphorylation, favoring the differentiation of anti-inflammatory cells such as Tregs and M2 macrophages, while limiting the development of pro-inflammatory phenotypes (e.g., Th1, Th17, M1 macrophages) (Noack & Miossec, 2014; Singh et al., 2014).

Considering that these findings are based on animal models, further research involving human subjects is necessary (Jia et al., 2021; Zhao et al., 2021). Moreover, it would be valuable to investigate metabolic changes more specifically in different T cell subsets (Jia et al., 2021; Zhao et al., 2021). The reduction in thyroid volume observed in the study by Jia et al. (Jia et al., 2021) has also been previously described (Dowling et al., 2011; Kimura et al., 2001). This effect may be attributed to the antiproliferative action of metformin through mTOR inhibition, as well as its indirect influence on thyroid gene expression via modulation of insulin and IGF-1 levels (Dowling et al., 2011; Kimura et al., 2001).

5. Conclusion.

Based on the studies discussed, metformin, in addition to its glucose-lowering effects, also exhibits immunomodulatory properties that may be relevant in the treatment of autoimmune diseases, including Hashimoto's thyroiditis. Its action on the AMPK/mTOR pathway, suppression of pro-inflammatory Th1 and Th17 lymphocytes, promotion of regulatory T cells (Tregs), and anti-inflammatory effects on macrophages and neutrophils suggest a potential role in modulating autoimmune processes.

However, the use of metformin in the therapy of Hashimoto's thyroiditis requires further well-designed clinical trials involving human subjects to evaluate its true effectiveness, safety, and therapeutic potential in modulating immune responses.

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Formal analysis: GK, WP
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Data curation: GS, JS
Writing - rough preparation: WP, GK
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