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Understanding the Challenges of Hashimoto's Thyroiditis: Perspectives on Diagnosis, Treatment, and Associated Conditions

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ABSTRACT:

Introduction: Hashimoto's thyroiditis is a prevalent autoimmune disease among the population. With the progress in diagnostic and research techniques, it has come to light that Hashimoto's thyroiditis is linked to a higher likelihood of developing other disorders that impact multiple organs and systems. Throughout the course of this disease, individuals may experience an array of complications such as sexual dysfunctions, fertility problems, specific mental disorders, cardiovascular diseases and other autoimmune diseases.

Aim of the Study: The primary aim of this study is to explore the potential association between Hashimoto's thyroiditis and its consequential effects on other physiological systems and organs.

Description of the State of Knowledge: Hashimoto's thyroiditis is a complex autoimmune disease characterized by chronic inflammation of the thyroid gland. The pathogenesis of the disease is not yet completely understood. Hashimoto's thyroiditis has been associated with a range of health issues, including sexual dysfunction, fertility problems, psychiatric disorders, cardiovascular diseases, and other autoimmune disorders.

Materials and methods: An unsystematic scientific literature review was conducted using specific keywords such as Hashimoto's thyroiditis, fertility problems, thyroid tumor, cardiovascular diseases, and autoimmune diseases. The review was carried out on PubMed, analyzing a total of 54 sources published until 2023.

Conclusions: HT's association with psychiatric disorders, fertility issues, thyroid tumors, cardiovascular dysfunction, and comorbid autoimmune conditions underscores its broad clinical impact, necessitating integrated management approaches. Effective management of HT requires collaboration among specialists to ensure early detection, proactive intervention, and patient education, ultimately improving therapeutic outcomes and quality of life.

KEY WORDS: Hashimoto's thyroiditis; fertility problems; thyroid tumor; cardiovascular diseases; autoimmune diseases; SLE; vitiligo; celiac disease; RA; T1D; diabetes

INTRODUCTION

Autoimmune diseases are a group of disorders that pose significant diagnostic and therapeutic challenges due to their unclear pathogenesis. It is estimated that approximately 5% of the global population suffers from autoimmune diseases [1], and healthcare professionals across various specialties may encounter affected patients. Autoimmune diseases occur when the body responds inappropriately to its own antigens, with women being more susceptible than men, and the clinical course of the disease varying between both genders [2].

An example of an autoimmune disease is Hashimoto's thyroiditis, which leads to hypothyroidism as the inflammatory reaction and organ destruction progress. The development of Hashimoto's thyroiditis (HT) is triggered by factors that cause dysregulation of the immune system, including infections, stress, and iodine intake [3]. As per the report by Xin-Liang Wang and his colleagues, there was an observed occurrence of HT in a pair of twins [10]. Diagnostically, the presence of antibodies against thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) is significant [4], and the disease clinically manifests with weight gain, cold intolerance, and constipation [5]. According to the medical literature, individuals diagnosed with HT may exhibit localized symptoms which include but are not limited to neck pain, discomfort in the throat area, dysphagia, dyspnea, sleep apnea, voice changes and pressure symptoms [9]. Although HT is treated with levothyroxine, most patients find it challenging to achieve stable disease control. It is imperative to prioritize the maintenance of a healthy lifestyle and to adopt a prudent approach towards dietary habits. The literature suggests that a specific diet rich in vitamin D, zinc, magnesium, and selenium, among other nutrients, can help stabilize the autoimmune process [6].

Research has shown that Hashimoto's thyroiditis (HT) is a probable risk factor for thyroid cancer. It has been observed that individuals diagnosed with HT who are scheduled for a biopsy

of a nodule on the thyroid gland are more likely to discover that the nodule is malignant. This information could be valuable for medical professionals who treat HT patients and those who conduct thyroid cancer screening [8].

HT is often associated with psychiatric disorders, fertility problems, thyroid tumors, cardiovascular diseases and other autoimmune diseases [7]. Therefore, further clinical studies are required to deepen our understanding of this area. It is of paramount importance to ensure that patients with HT are vigilantly monitored for the potential development of the aforementioned conditions.

HASHIMOTO'S THYROIDITIS AND PSYCHIATRIC DISORDERS

Thyroid diseases often exhibit symptoms associated with psychiatric disorders. For instance, Hashimoto's thyroiditis may cause symptoms such as low mood, fatigue, difficulty concentrating, decreased motivation, and reduced interest in various activities that closely resemble depressive disorders [11]. This may pose significant challenges in diagnosing the disease correctly and initiating appropriate treatment. Merely measuring thyrotropin and thyroid hormones may not be enough to identify thyroid dysfunction in patients exhibiting these symptoms. Reports suggest that high levels of anti-thyroid peroxidase antibodies (anti-TPO) may increase the risk of developing depression in patients with Hashimoto's disease, regardless of thyroid gland function impairment [12]. Patients with severe, atypical, or treatment-resistant depression require special attention.

Women with depressive disorders occurring at specific life stages, such as early pregnancy, postpartum, or perimenopausal periods, have shown an association with autoimmune disease [13]. During the third trimester of pregnancy, when there is a strong suppression of the maternal immune system, the prevalence of depressive disorders decreases along with a reduced number of patients with elevated levels of anti-TPO antibodies [14]. Chronic illness in patients with Hashimoto's thyroiditis can also cause depressive symptoms. Various somatic symptoms such as weight gain, hair loss, constipation, dry skin, and complications related to the course of Hashimoto's thyroiditis can further exacerbate low mood and reduce the quality of life.

Bipolar affective disorder is another disorder associated with Hashimoto's thyroiditis. There are documented cases of patients with untreated hypothyroidism experiencing episodes of acute mania with characteristic symptoms during the ongoing autoimmune process. The manic episode symptoms subsided after combined treatment with mood stabilizers/antipsychotics and levothyroxine [15]. Studies conducted on twins have shown a significantly greater susceptibility to developing anti-thyroid antibodies in the offspring of patients with bipolar affective disorder.

Anxiety disorders are more common in patients with Hashimoto's thyroiditis and thyroid goiter than in the general population. The most commonly described symptom is obsessive-compulsive disorder (OCD), which affected 15.7% of the surveyed population [16]. Researchers have also shown an increased risk of sleep disorders, generalized anxiety disorders, and social phobias [12]. Hashimoto's encephalopathy is another dangerous phenomenon with symptoms including fluctuating consciousness disturbances, hallucinations, acute or subacute neurological symptoms, and coma. These symptoms subside after treatment with glucocorticosteroids and levothyroxine. Increased levels of anti-thyroid antibodies have been observed in the serum or cerebrospinal fluid of examined patients. A good response to glucocorticosteroid (GCS) treatment may also underscore the etiology of autoimmune disease [17].

Finally, it is essential to remember that besides periodically measuring hormones such as thyrotropin (TSH), thyroxine (T4), and triiodothyronine (T3), an assessment of patients' mental status should be conducted to promptly diagnose concurrent psychiatric disorders and initiate

appropriate treatment. Although the correlation between autoimmune processes in thyroid diseases and increased occurrence of psychiatric disorders is not fully understood, it requires further evaluation.

HASHIMOTO'S THYROIDITIS AND FERTILITY – FEMALE FERTILITY, MALE FERTILITY, MANAGEMENT AND TREATMENT

Although Hashimoto disease is primarily associated with thyroid dysfunction, its impact extends beyond the thyroid, affecting various aspects of health, including reproductive capability in both men and women. Understanding how Hashimoto's disease affects fertility is crucial for individuals confronting reproductive challenges.

In women, Hashimoto's disease can disrupt fertility through multiple mechanisms. Thyroid hormones, particularly thyroxine (T4) and triiodothyronine (T3) play crucial role in regulating the menstrual cycle and ovulation. They influence the development of ovarian follicles, the maturation of oocytes, and the maintenance of the uterine lining necessary for implantation and pregnancy.

Imbalances in thyroid hormone levels can disrupt these processes, leading to difficulties in conceiving and maintaining a pregnancy [18]. In women of fertile age, hypothyroidism results in changes in cycle length and amount of bleeding such as oligomenorrhea, amenorrhea, polymenorrhea, and menorrhagia and it's connected with diminished libido [19]. Moreover, women with autoimmune thyroiditis might be at risk of ovarian insufficiency due to decreased ovarian reserve. Furthermore, Hashimoto's disease is associated with an increased risk of miscarriage, mainly in the first trimester, due to higher maternal TSH concentration [20]. Thyroid hormones play a crucial role in fetal development, particularly during the first trimester when the fetus relies entirely on the mother's thyroid hormones. Moreover, women with untreated or poorly managed Hashimoto's disease may have higher rates of preterm birth, and other pregnancy complications such as anemia, preeclampsia, placental abruption, postpartum hemorrhage, and cardiac dysfunction [21, 22]. Consequently, patients with positive anti-thyroid peroxidase (TPO) antibody findings, who wish to start a family, should be aware of their lower reproductive life span. While thyroid irregularities are more prevalent in women than men and research on the direct impact of Hashimoto's disease on male fertility is limited, emerging evidence suggests that thyroid dysfunction can also affect male reproductive health [23, 24]. Thyroid hormones play a significant role in spermatogenesis and impaired thyroid function may lead to decreased sperm quality and quantity, especially abnormal number and motility of sperm [25]. Additionally, thyroid dysfunction can disrupt the hypothalamic-pituitary-gonadal (HPG) axis, which may lead to decreased testosterone levels [26] causing delayed ejaculation, dysfunction of erection, premature ejaculation, and reduced libido [27, 28]. Given the lasting impacts of thyroid irregularities on male reproductive health and sexual function, it's important to promptly screen and address thyroid disorders in men experiencing sperm issues and erectile dysfunction, aiming to maintain and enhance their overall well-being [23].

For individuals with Hashimoto's disease who are dealing with fertility issues, proper management and treatment are essential. The guidelines of the American Endocrine Society, and American Association of Clinical Endocrinologists and American Thyroid Association recommend thyroxine (T4) substitution [29]. In women, achieving optimal thyroid hormone levels is crucial before conception to improve fertility outcomes and reduce the risk of pregnancy complications. Regular monitoring of thyroid function throughout pregnancy is also recommended.

HASHIMOTO'S THYROIDITIS AND THYROID TUMORS

Clinicians should take into consideration the possibility that HT could contribute to thyroid cancer development, as it is the most common cause of hypothyroidism in developed countries. The findings showed a strong association between HT and thyroid cancers, including PTC, MTC, and lymphoma, but not ATC or FTC [30]. Many theories have been put out, but it is unknown how Hashimoto's thyroiditis and carcinogenesis are related. Numerous studies have demonstrated the close relationship between inflammation and cancer occurrence, as well as the critical role it plays in the initiation and progression of cancer [31]. Xu et al. explained their findings by three potential pathogenic pathways. The inflammatory reaction, in the first place, fosters the conditions necessary for malignant transformation. Epithelial cells may undergo malignant transformation as a result of alterations in stromal responsiveness brought on by cytokines and growth factors' harm to stromal cells. Furthermore, immune cells invading the thyroid gland may encourage aberrant DNA repair, which would cause PTC. Second, TSH stimulates the production of thyroid hormones naturally and acts as a growth factor for thyroid cells. For the majority of HT patients, elevated TSH causes follicular epithelial hyperplasia, which in turn encourages PTC [32, 33]. Third, the transition from HT to PTC may be mediated by the expression of certain oncogenes, such as p63 mutation and RET/PTC gene rearrangement. Contrarily, PTC without HT is more likely to have the BRAFV600E mutation, which is typically mutually exclusive with RET/PTC gene rearrangement [34]. There is a strong negative correlation between coexisting HT and PTC-related mortality, as well as between coexisting HT and structural recurrence and the current tumor's aggressiveness. These results point to HT's potential preventive function against the advancement of PTC [35]. Patients with Hashimoto thyroiditis (HT) are less likely to experience recurrence than PTC patients without HT because they are more likely to have multifocal carcinomas, which require more invasive and drastic surgery.

There was a clear correlation between HT and non-Hodgkin primary thyroid lymphoma, with a risk approximately 60 times higher than in the general population. Roughly 5 percent of thyroid neoplasms are thyroid lymphomas. Establishing a thyroid lymphoma diagnosis is crucial because it shifts the first line of treatment for lymphoproliferative disorders from adequately focused chemotherapy to surgery, which is often used for malignant thyroid nodules [36].

Compared to patients without HT, those with HT exhibited superior clinical features and a more favorable prognosis. Because individuals with HT are more likely to experience anxiety and have frequent thyroid gland ultrasounds, it is more likely that a cancerous thyroid nodule will be found early on [37].

HASHIMOTO'S THYROIDITIS AND CARDIOVASCULAR SYSTEM FUNCTION

Hashimoto's thyroiditis is a thyroid gland condition that can have significant implications for cardiovascular function. Thyroid hormones are involved in various physiological processes, including metabolism, lipid synthesis, and heart function. The hormones aid in the regulation of heart function by enhancing the expression of beta receptors in cardiac muscle and the vascular system, which results in increased heart rate, cardiac output, and contractility [38].

Research has revealed that in Hashimoto's disease, marked by high levels of TSH and low levels of T3 and T4 hormones due to chronic thyroid inflammation, the T3 hormone activates the endothelial nitric oxide (NO) signaling pathway. This pathway is critical in maintaining vascular balance and exerting a dilatory effect, thus decreasing vascular constriction [39]. However, this can cause elevated diastolic blood pressure due to decreased endothelial relaxation.

Hashimoto's thyroiditis can disrupt homeostasis, accelerate the progression of cardiovascular diseases, or worsen their course [40]. It often leads to symptoms such as angina, decreased heart

sounds, diastolic hypertension, sinus bradycardia, and atrioventricular blocks I-III [41]. Electrocardiographic recordings may show low QRS complex voltage, QT interval prolongation, and ST-T segment changes, such as flattening or inversion of the T wave or ST-T segment depression. Conduction disturbances may also occur, and QT interval prolongation predisposes to ventricular arrhythmias [42]. Patients with Hashimoto's thyroiditis may experience impairment of left ventricular function, increased vascular resistance, and both systolic and diastolic heart failure, resulting in a decrease in cardiac output by 30-50%. In severe cases, they may experience coronary artery disease, decreased myocardial contractility, reduced stroke volume, pericarditis, and pericardial effusion. The latter is caused by increased pericardial permeability with simultaneous decrease in lymphatic drainage of albumin, leading to protein shifting into the pericardial space and fluid accumulation [43]. Such fluid accumulation is, however, rare and slow enough to allow the heart to adapt to changes without causing significant hemodynamic disturbances.

Thyroid hormones have a multifaceted impact on organ systems, including the cardiovascular system. The main mechanisms of action on the heart are observed through changes in heart rate, myocardial contractility, blood pressure regulation, lipid metabolism, and modulation of inflammatory pathways (Figure 1) [44].

Effective treatment of disorders in patients with Hashimoto's thyroiditis requires interdisciplinary collaboration between endocrinology and cardiology specialists.

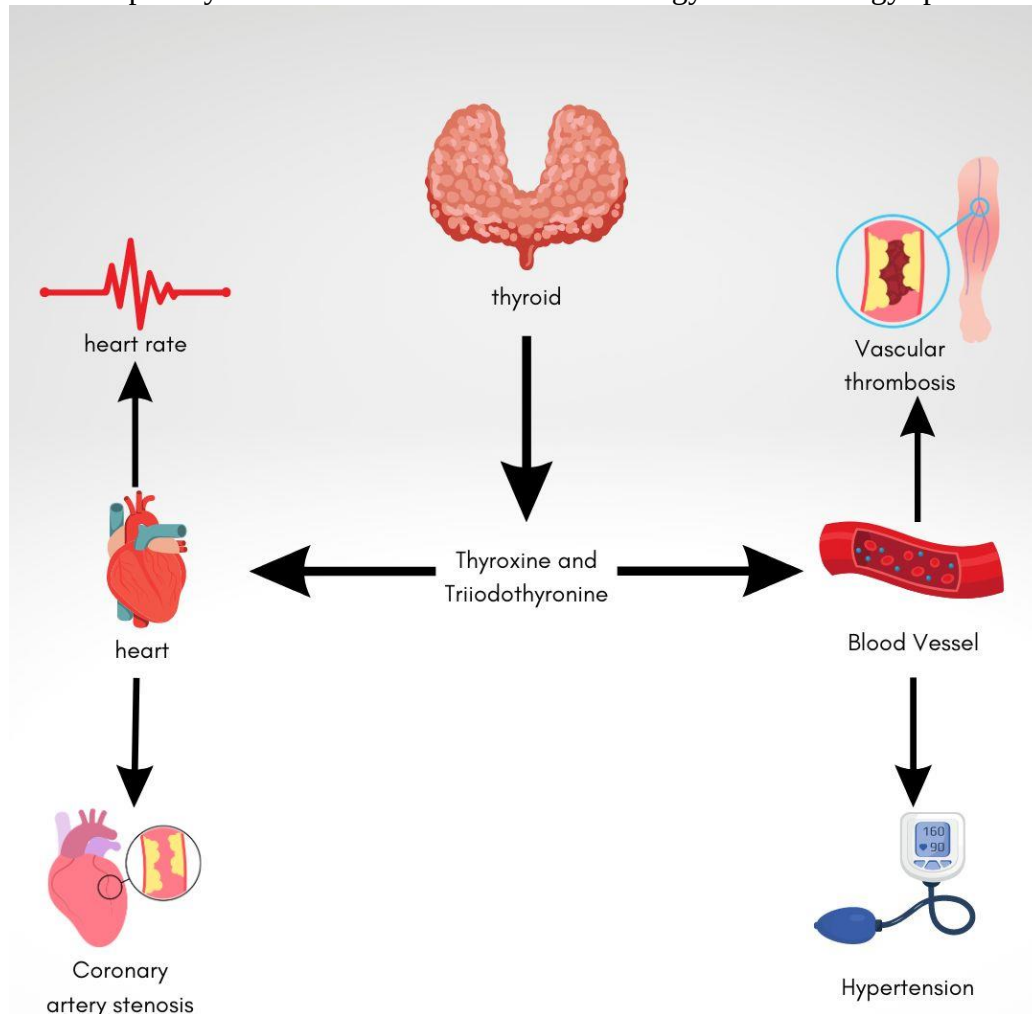


Figure 1. Impact of thyroid hormones on the cardiovascular system. Based on own elaboration [7].

HASHIMOTO'S THYROIDITIS AND OTHER AUTOIMMUNE DISEASES – T1D, RA, CELIAC DISEASE, VITILIGO, SLE

Chronic autoimmune thyroiditis often predisposes to other autoimmune diseases, such as type 1 diabetes, celiac disease, rheumatoid arthritis, systemic lupus erythematosus, and vitiligo. Autoimmunity disorders have a common pathomechanism of attacking the body's own, healthy cells and tissues. A special role is assigned to the HLA-DQ2 and DQ8 haplotypes (which are over-presented) and the CD40, CTLA4, PTPN22 proteins, as well as the TSH and thyroglobulin receptor genes. These proteins and genes are inherited, which increases the risk of disease's occurrence in probands. Disease duration over five years and female gender are associated with an increased risk of developing another autoimmune disease [45].

Rheumatoid arthritis is a chronic systemic inflammatory disease symmetrically affecting mainly peripheral joints, more often affecting women. The common mechanism of RA and HT is autoimmunity. Research shows that the STAT4, HLA-DRB1 genes and vitamin D receptors (present in B and T lymphocytes) play a particularly important role in the development of both diseases. A correlation between the occurrence of a positive anti-TPO antibody titer and the exacerbation and more severe clinical course of RA has also been documented [46, 47].

Type 1 diabetes is a metabolic disorder associated with the destruction of insulin-producing pancreatic β cells by autoantibodies. Thyroid hormones play a key role in the metabolism of lipids and carbohydrates, and thyroid hormone receptors are particularly important in the proper development of pancreatic islets. Studies indicate a close connection between the co-occurrence of HT and D1M, compared to the general population, insulin-dependent diabetes is more common in people with Hashimoto's disease and vice versa. T1D most often develops in childhood, studies indicate that 25% of children with D1M also develop HT, and the co-occurrence of HT exacerbates the course of T1D [48]. The pathomechanism of both diseases is related to their similar immunogenetic sensitivity. HLA, AIRE, PTPN22, FOXP3, CTLA-4 genes, as well as VD and CXCL deficiency and infections significantly influence the appearance and course of both of these diseases. The co-occurrence of both diseases is more often observed in the female sex. The predominance of these conditions in women suggests that etiological risk components unrelated to D1M are correlated with HT. It is suggested that these are female sex hormones, reproductive history. The coexistence of Hashimoto's thyroiditis and type 1 diabetes is common in people suffering from polyendocrinopathy (AP), and often correlates with a positive family history, which is associated with a predisposition to the development of hereditary autoimmunity [49].

Celiac disease (gluten-dependent celiac disease) is a chronic, multi-organ autoimmune disease in which, in genetically predisposed people, the small intestine is damaged by consuming gluten. Celiac disease and HT have a common immunopathogenetic basis, associated with the overrepresentation and inheritance of HLA-DQ2 and DQ8 haplotypes. Common HLA genotypes correlate with IgA deficiency and celiac disease. People affected by HT have an increased risk of gluten intolerance and intestinal villi atrophy, while in people suffering from celiac disease, an increased risk of autoimmune thyroid diseases has not been officially confirmed [50].

Vitiligo is a chronic autoimmune disease involving depigmentation of patches of skin. Studies show that thyroid dysfunction significantly correlates with the etiopathogenesis of vitiligo. People affected by vitiligo have a significant increase in anti-TG and anti-TPO antibodies compared to the general population. Mutations of the Forkhead D3 (FOXD3) transcription factor (occurring much more often in people with vitiligo) and the simultaneous occurrence of elevated antithyroid antibodies are also strongly associated [51]. The second hypothesis linking both of these diseases is the theory of oxidative stress, which indicates significant amounts of

reactive oxygen species damaging thyrocytes and melanocytes, the target molecules of which have a common origin – tyrosine [52].

Systemic lupus erythematosus (SLE) is an autoimmune disease developing as a result of complex disorders of the immune system, leading to a chronic inflammatory process in many tissues and organs, women suffer from the disease 6-10 times more often than men. Retrospective studies have shown that patients with SLE are twice as likely to suffer from HT compared to the general population. Clinical studies have shown significant increases in anti-TPO and anti-TG thyroid antibodies in these patients, and anti-Sm antibodies significantly correlate with this. However, SLE exacerbations, disease activity and the degree of organ damage do not correlate with HT or the presence of anti-TG and anti-TPO antibodies [53, 54].

CONCLUSIONS

1. Autoimmune diseases: The prevalence of autoimmune diseases underscores the need for continued research into their pathogenesis and management. The complex interplay between genetic predisposition, environmental triggers, and immune dysregulation highlights the multifaceted nature of these disorders.
2. Hashimoto's Thyroiditis (HT) and Psychiatric Disorders: The association between HT and psychiatric disorders, including depression, bipolar affective disorder, anxiety disorders, and Hashimoto's encephalopathy, emphasizes the importance of comprehensive patient assessment and management strategies integrating both endocrinological and psychiatric care.
3. HT and Fertility: Understanding the impact of Hashimoto's disease on fertility is crucial for individuals planning families. Both women and men face potential challenges, necessitating proactive management to optimize reproductive outcomes and reduce the risk of miscarriage and other complications during pregnancy.
4. HT and Thyroid Tumors: The relationship between HT and thyroid cancer warrants attention in clinical practice, with evidence suggesting a significant association, particularly with papillary thyroid carcinoma (PTC) and thyroid lymphoma. Further research is needed to elucidate the underlying mechanisms and implications for patient management.
5. HT and Cardiovascular Function: Hashimoto's thyroiditis can adversely affect cardiovascular health, emphasizing the importance of vigilance for cardiac manifestations in affected individuals. Collaborative efforts between endocrinologists and cardiologists are essential for comprehensive patient care.
6. HT and Other Autoimmune Diseases: The co-occurrence of HT with other autoimmune conditions such as type 1 diabetes, rheumatoid arthritis, celiac disease, vitiligo, and systemic lupus erythematosus underscores the need for integrated approaches to diagnosis and management. Genetic predisposition and shared immunopathogenic mechanisms contribute to the complex interplay between these disorders.

In conclusion, addressing the challenges posed by Hashimoto's thyroiditis and its associated comorbidities requires a multidisciplinary approach, encompassing clinical care, research, and patient education. By advancing our understanding of these conditions and implementing comprehensive management strategies, healthcare professionals can improve outcomes and quality of life for affected individuals.

DISCLOSURE

Author's contribution
Klaudia Brygida Kułak: Conceptualization, writing rough preparation,

Karolina Alicja Palacz: Writing rough preparation, formal analysis,
Katarzyna Gadżala: supervision, resources
Izabela Janik: visualization, data curation
Marzena Pliszka: Methodology, software,
Katarzyna Chamera-Cyrek: check, investigation,
Anna Maria Koman: writing and editing, project administration.

Project administration: Karolina Alicja Palacz

All authors have read and agreed with the published version of the manuscript.

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The authors deny any conflict of interest

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