

SYSTEMIC CHRONIC LOW-GRADE INFLAMMATION AND THE DEVELOPMENT OF THYROID AUTOANTIBODIES: IMMUNOLOGICAL MECHANISMS AND BIOMARKER PERSPECTIVES

SISTEMSKA HRONIČNA UPALA NISKOG STEPENA I RAZVOJ AUTOANTITELA NA ŠTITNU ŽLEZDU: IMUNOLOŠKI MEHANIZMI I PERSPEKTIVE BIOMARKERA

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Summary

Thyroid autoantibodies, chiefly antibodies against thyroid peroxidase (TPOAb), thyroglobulin (TgAb), and the thyroid-stimulating hormone receptor (TRAb), are central serological hallmarks of autoimmune thyroid disease (AITD). Their presence may precede overt hypothyroidism or hyperthyroidism by years, yet the systemic conditions that facilitate their emergence remain incompletely understood. Systemic chronic low-grade inflammation (SCLGI), a persistent and subclinical inflammatory state characterized by modest elevations in circulating cytokines, acute-phase reactants, and innate immune activation, has emerged as a plausible upstream contributor. Obesity, insulin resistance, aging, dysbiosis, chronic psychosocial stress, and cardiometabolic disease all promote SCLGI and may lower the threshold for thyroid-directed loss of tolerance. This review synthesizes current evidence linking SCLGI to thyroid autoantibody development, emphasizing cytokine-driven antigen presentation, Th1/Th17–Treg disequilibrium, B-cell activation, oxidative stress, and altered mucosal immune signaling. We further evaluate the potential of conventional inflammatory indicators, cytokine panels, hematologic ratios, adipokines, and composite multi-omics signatures as biomarkers for risk stratification. Existing evidence is biologically coherent but remains largely cross-sectional; therefore, longitudinal studies that distinguish autoantibody initiation from progression to clinical disease are urgently required. A biomarker-guided framework integrating inflammatory burden with genetic,

Kratak sadržaj

Autoantitela usmerena protiv štitne žlezde – prvenstveno antitela protiv tiroidne peroksidaze (TPOAb), tiroglobulina (TgAb) i receptora za tireostimulišući hormon (TRAb) – predstavljaju ključne serološke odlike autoimunskih oboljenja štitne žlezde (AITD). Njihovo prisustvo može godinama prethoditi pojavi manifestne hipotireoze ili hipertireoze, dok mehanizmi koji pogoduju njihovom nastanku u okviru sistemskih poremećaja još uvek nisu u potpunosti razjašnjeni. Sistemska hronična upala niskog intenziteta (SCLGI) – perzistentno, subkliničko upalno stanje koje karakterišu umereno povišeni nivoi citokina u cirkulaciji, reaktanata akutne faze i aktivacija urođenog imuniteta – prepoznata je kao verovatan uzročni faktor koji prethodi ovim procesima. Gojaznost, insulinska rezistencija, starenje, disbioza, hronični psihosocijalni stres i kardiometaboličke bolesti doprinose razvoju SCLGI i mogu sniziti prag za gubitak imunološke tolerancije prema štitnoj žlezdi. Ovaj pregledni rad sumira trenutne dokaze koji povezuju SCLGI sa razvojem autoantitela protiv štitne žlezde, sa posebnim osvrtom na prezentaciju antigena posredovanu citokinima, neravnotežu između Th1/Th17 i Treg ćelija, aktivaciju B-limfocita, oksidativni stres i izmenjenu imunološku signalizaciju na nivou sluzokože. Takođe razmatramo potencijal konvencionalnih pokazatelja upale, panela citokina, hematoloških odnosa, adipokina i složenih »multi-omiks« profila kao biomarkera za procenu rizika. Postojeći dokazi su biološki konzistentni, ali se uglavnom zasnivaju na studijama preseka; stoga su hitno potrebne longitudinalne studije koje bi

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metabolic, and thyroid-specific factors may improve early identification and prevention of AITD.

Keywords: chronic low-grade inflammation, thyroid autoantibodies, autoimmune thyroid disease, TPOAb, TgAb, biomarkers, obesity, immune tolerance

Introduction

Autoimmune thyroid disease (AITD) is a group of diseases where various organs show abnormalities due to loss of immune tolerance towards thyroid antigens. The two main clinical types are Hashimoto thyroiditis (HT) and Graves' disease (GD). Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) are most frequently associated with HT, and the stimulation or blocking of thyrotropin receptor antibodies (TRAb) is directly involved in the development of GD (1, 2). Autoantibodies are not only signs of illness; they may also be indicators of the start of thyroid failure in vulnerable people, and some are known to predict a certain level of risk for women during pregnancy, after immune system problems, or following exposure to harmful environments (3–5).

The old way of thinking about autoimmune thyroid disease (AITD) is genetic predisposition, differences in immune regulation for men and women, environment and thyroid diseases. Alleles of human leukocyte antigens, CTLA-4, PTPN22, IL2RA and others are risk factors, and iodine excess, smoking, infection signals, selenium status, certain drugs and immune changes in pregnancy can alter disease expression (1, 5). However, these reasons do not fully explain why autoimmune diseases are more frequent in metabolically unhealthy individuals or why the antibody profiles of different people vary so widely. Systemic chronic low-grade inflammation (SCLGI) is a general-purpose explanation, though not an exclusive one.

SCLGI denotes persistent activation of inflammatory pathways without the clinical features of acute infection. It is commonly reflected by modestly increased high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), IL-1 β , chemokines, and activation of innate immune cells (6, 7). Adipose tissue expansion, ectopic lipid deposition, gut barrier dysfunction, cellular senescence, sleep disturbance, and chronic stress can sustain this state (6–8). Unlike transient inflammation, SCLGI may repeatedly expose autoreactive lymphocytes to costimulatory and cytokine signals, thereby promoting breach of peripheral tolerance.

napravile razliku između početnog stvaranja autoantitela i progresije ka klinički manifestnoj bolesti. Primena okvira zasnovanog na biomarkerima, koji objedinjuje podatke o upalnom opterećenju sa genetskim, metaboličkim i specifičnim faktorima vezanim za štitnu žlezdu, mogla bi unaprediti rano otkrivanje i prevenciju AITD.

Ključne reči: hronična zapaljenja niskog intenziteta, autoantitela na štitnu žlezdu, autoimunska bolest štitne žlezde, TPOAb, TgAb, biomarkeri, gojaznost, imunološka tolerancija

This review examines the immunological routes through which SCLGI may facilitate thyroid autoantibody development and critically discusses biomarkers that could identify this transition before overt thyroid disease. Particular attention is given to the distinction between association and causation, because thyroid dysfunction itself can alter inflammatory and metabolic indices.

Thyroid Autoantibodies and the Preclinical Continuum of AITD

TPO is a membrane-bound enzyme necessary for the production of thyroid hormones and is highly immunogenic in HT. Tg is the main iodinated protein substrate in the follicular lumen. Antigens can be recognized by various antibodies, but they have different sensitivities and levels of pathogenicity and tissue damage (1, 2). The presence of TPOAb is a certain indicator of autoimmune hypothyroidism, and although TgAb may enhance diagnostic sensitivity under certain circumstances, it is often negative in patients with no other symptoms or differentiated thyroid cancer (3). TRAb has many functions. TRAb stimulates the TSH receptor in the thyroid and is the cause of hyperthyroidism in GD; antibody blockade leads to hypothyroidism (2).

The change in immune susceptibility, autoantibody positivity and overt AITD is usually not a gradual one. The genetically susceptible person may be antibody-negative after exposure to the environment, and the other person can have low-titer antibodies that do not cause biochemical disease. Hypothyroid patients are likely to have a certain degree of lymphoplasmacytic infiltration, stress of the thyrocyte, and loss of functional reserve. GD is the expression level of TRAb function, intrathyroidal immune response and receptor signalling that affects phenotype (1, 2). Therefore, the appearance of an antibody should be considered as part of the whole immune-metabolic network and not just a lab result.

The above are reasons why the thyroid is susceptible to inflammation. The synthesis of hormones needs to produce hydrogen peroxide and perform many iodinations; thus, if antioxidant

defence is weak, there will be oxidative stress. With the addition of cytokines, the thyroid cells will increase their expression of MHC class II molecules and release chemokines to draw immune cells (5, 9). In the pro-inflammatory state of the whole body, these local factors may lead to the turnover of thyroid antigens and thus become immunogenic antigens.

Biological Features and Sources of Systemic Chronic Low-Grade Inflammation

Systemic chronic low-grade inflammation (SCLGI) is often the result of a combination of changes in metabolism, weakened immunity and damaged tissues. Obesity is related to the hypertrophy of adipocytes and the release of free fatty acids, leptin, damage-associated molecular patterns, etc., and at the same time, infiltrating macrophages and other immune cells release TNF- α , IL-6, IL-1 β and monocyte chemoattractant protein-1 (6, 7). Saturated fatty acids and microbial products can activate pattern-recognition receptors by way of activation; that is to say, they activate Toll-like receptors and then trigger NF- κ B signalling and the inflammasome in the nucleus (7, 10). Insulin resistance is both a cause and a result of this inflammatory circuit.

The microbiota in the intestine also regulates it. Under conditions of gut barrier dysfunction — promoted by a Western-type diet, antibiotic exposure, chronic stress and obesity — the integrity of the intestinal epithelial tight junctions is compromised, allowing microbially produced lipopolysaccharide (LPS), peptidoglycan and microbial DNA to translocate from the gut lumen into the portal and systemic circulation (8, 11). LPS binds Toll-like receptor 4 (TLR4) on macrophages, dendritic cells and thyrocytes, activating NF- κ B and the NLRP3 inflammasome and thereby increasing systemic IL-6, TNF- α and IL-1 β production, a state termed low-grade endotoxemia (8, 11). In parallel, microbial metabolites such as short-chain fatty acids (SCFAs) — primarily butyrate and propionate — enter the bloodstream and act through G-protein-coupled receptors (GPR43, GPR109A) and histone-deacetylase inhibition to shape T-cell differentiation, and reduced SCFA-producing bacteria may weaken regulatory T-cell (Treg) maintenance and disturb the Th17/Treg balance. Bacterial components that structurally resemble thyroid antigens may further engage cross-reactive T and B cells through molecular mimicry, and human cohort studies have repeatedly reported altered gut microbial composition in Hashimoto's thyroiditis (HT) and Graves' disease, including reduced diversity and depletion of butyrate-producing genera such as *Lactobacillus*, *Bifidobacterium* and

Faecalibacterium. Although most of these studies are cross-sectional and cannot distinguish cause from consequence, they support a gut-immune-thyroid axis in which microbial metabolites enter the systemic circulation and disrupt thyroid immune tolerance. Nutritional pattern, antibiotic exposure and obesity may further modify this axis (12).

Aging is associated with immunosenescence and inflammaging. Senescent cells release inflammatory mediators, and with age, there are also changes in blood cell production, T-cell repertoire and regulatory immune function that can disrupt tolerance (13). Chronic psychosocial stress, lack of sleep and physical inactivity can also change the activity of the hypothalamic–pituitary–adrenal axis, sympathetic nervous system, cytokines and metabolism (14). Not only is there one exposure, but several will also be accumulated gradually.

SCLGI is not an abnormal indicator itself; some people will have normal hs-CRP levels even if there are cytokine or cellular immunity problems, and there are many changes in cytokines in the lab. Therefore, it is more reasonable to view the construct as having many dimensions instead of as a single-choice diagnosis.

Immunological Mechanisms Linking SCLGI to Thyroid Autoantibody Generation

Throughout this section, mechanistic evidence is presented at three levels — in vitro experiments, animal models and human observational studies — and these levels are distinguished explicitly wherever possible. In vitro and animal data establish biological plausibility but cannot prove that the same cascade operates in patients; human data are mostly cross-sectional and therefore cannot establish the temporal sequence between SCLGI and thyroid autoantibody seroconversion.

Enhanced antigen presentation and costimulation

Loss of tolerance occurs not only when there are antigens but also requires antigen presentation in the presence of an immunostimulatory environment. IL-1 β , TNF- α , IFN- γ and Type I interferon can induce the differentiation of antigen-presenting cells and increase the expression of MHC and costimulatory molecules (15). IFN- γ can increase the expression of MHC class II on thyrocytes in the thyroid gland and make them participate in local antigen presentation during inflammation (9). Therefore, there may be more repeated systemic inflammatory signals, and thus the risk of TPO- and Tg-derived peptides being presented by autoreactive T cells that have evaded central deletion is high. However,

the evidence for this cascade derives largely from in vitro and animal experiments, whereas direct demonstration in human thyroid tissue remains limited to descriptive observations; whether repeated systemic inflammatory signals precede antibody seroconversion in humans is not yet established.

Oxidative stress can change the proteins in thyrocytes, damage the cells, release altered antigens from inside and outside the cell, and thus increase immunogenicity. Overactivity of the thyroid gland can lead to an excess of reactive oxygen species (ROS) through hormone synthesis, inflammatory cell infiltration and other reasons (16). Oxidatively modified self-antigens can be broken down in different ways and promote epitope spreading; it is one of the ways the immune system recognizes more thyroid epitopes than the initial determinant.

Innate immune activation and inflammasome signaling

Receptors of the innate immune system are triggered by changes in metabolism or microbes. Macrophages, dendritic cells, B cells and thyrocytes have toll-like receptors (TLRs) that bind PAMPs and DAMPs. TLR activation of NF- κ B promotes the production of IL-6, TNF- α and pro-IL-1 β (10, 15). Then the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome can mature IL-1 β and IL-18 in response to signals of cell damage.

Therefore, it is suitable for autoimmunity, and IL-1 β can promote the activation of endothelial cells, leukocyte recruitment and differentiation of inflammatory T cells, etc. Continued activation of the innate immune system in the experimental and clinical cases of autoimmune diseases may provide a "boost" by increasing the likelihood that self-antigens will induce a prolonged adaptive immune response (15, 17). Although the exact mechanisms of thyroid disease in humans have not been fully revealed yet, an increase in innate immune factors has been shown in the tissues and peripheral immune cells of AITD (17). Therefore, SCLGI may be a lenient systemic background rather than the main reason for thyroid damage. Importantly, these findings derive mainly from experimental models and descriptive human tissue analyses; cross-sectional studies in patients cannot establish whether innate immune activation precedes antibody development.

Th1/Th17 predominance and impaired regulatory T-cell control

For a long time, it has been believed that HT belongs to the Th1-type, and damage to thyrocytes is caused by IFN- γ -related cell-mediated immunity. GD also has a complex T-cell response and cannot

be divided into one kind of helper T-cell pathway (1,18). Recently, T helper 17 (Th17) cells and their associated cytokine IL-17 have also been associated with the AITD phenotype. IL-6, IL-1 β and IL-23 are often raised in SCLGI, and if there is no regulatory signal, they can promote the differentiation and stabilisation of Th17 cells (18, 19).

Regulatory T cells (Tregs) have the function of suppression and generally express FOXP3; they are needed to limit the activity of self-reactive T cells. Defects in Treg numbers, phenotypes, trafficking and suppression have been reported in AITD; however, the results vary with different stages of the disease, treatment status and assays (20). Metabolic inflammation changes the function of regulatory T cells (Tregs) through the secretion of cytokines and other modifications to leptin signaling, oxidative stress, nutrient-sensing pathways, etc. A decrease in the Treg/effector ratio will result in an increase in the number of rare thyroid-reactive clones and the development of autoreactive B cells.

The Th17-Treg axis is associated with organ-specific autoimmunity of cardiometabolic inflammation. It should not be assumed that it is generally applicable. The number of peripheral blood cells is not affected by thyroid-draining lymph nodes or intrathyroidal lesions, and cross-sectional immune profiling cannot distinguish whether the imbalance is due to or a result of existing autoimmune diseases. These caveats apply to most peripheral-blood immune profiling studies, which reflect systemic rather than thyroid-specific immune status.

B-cell activation, ectopic lymphoid organization, and antibody maturation

The development of autoantibodies needs the activation of B cells, antigen recognition, T-cell assistance, and then the differentiation of antibody-secreting cells. Inflammatory cytokines can reduce the activation threshold of B cells and increase the survival rate of autoreactive clones. B-cell activating factor of the TNF family (BAFF) is especially important because it promotes the survival of B cells and has been associated with many autoimmune diseases (21). Some more BAFF signals can help autoreactive B cells that would have been deleted or anergised survive.

IL-6 promotes the differentiation of plasma-blasts and Ig production; IL-21 from T follicular helper cells is needed for the formation of germinal centres and affinity maturation. Chronic inflammation can also be one of the reasons for the formation of ectopic lymphoid structures in the target organ and create a favourable microenvironment for antigen presentation and B-cell selection (22). HT

is composed of intrathyroidal lymphoid aggregates with germinal centre morphology and produces autoantibodies at this site. Antibodies that develop as a result can promote the progression of the disease in various ways, such as complement activation, antibody-dependent cellular cytotoxicity, receptor modulation, etc., and are also signs of persistent pathological T-cell activity (1, 22). The role of B-cell survival factors such as BAFF in human AITD is supported by cross-sectional measurements of circulating BAFF and by histological observations of intrathyroidal germinal centres, but longitudinal data confirming that these changes precede seroconversion are still lacking.

Adipokines and the metabolic-immune interface

Leptin, adiponectin, resistin and other adipokines signal about the nutritional status of immune cells. Leptin promotes the development of pro-inflammatory T cells and reduces Treg proliferation; adiponectin is generally anti-inflammatory, but its effect on various tissues and in different forms varies (23). Therefore, hyperleptinemia in obesity may promote the polarisation of Th1/Th17 cells and B cells. Observational studies have found changes in the adipokine profile of AITD, but due to the effect of thyroid hormone status on body composition and adipokine secretion, it is not clear whether these changes are positive or negative clinically (24).

Insulin resistance can also increase the secretion of cytokines to cause autoreactivity, damage mitochondria and change the metabolic state of immune cells. Activated lymphocytes change their metabolic state, and if there is an excess supply of nutrients, they will either be effector cells or regulatory cells. These links are plausible, but they do not provide direct proof that insulin resistance is the cause of TPOAb or TgAb production. As in the other mechanistic subsections, these associations are derived from a mixture of experimental models and cross-sectional human studies, and causality cannot be inferred from the human data alone.

Evidence from Human Studies: Associations, Heterogeneity, and Causality

In studies on the population, thyroid autoimmunity is often linked to metabolic syndrome, inflammation, obesity, etc., but the results are inconsistent. Some groups have reported that there is a higher prevalence or titre of TPOAb in people with overweight and obesity, insulin resistance, metabolic syndrome, etc.; other studies have not found an association or have found a sex-specific association (25, 26). Differences in iodine intake, age

structure, reproductive status, ethnicity, medication use, antibody cutoffs and exclusion of overt thyroid disease may be the reasons for the inconsistency.

Confounding and reverse causation must be considered when interpreting these inconsistent results. Iodine intake is a major effect modifier: in iodine-deficient regions, goitre and fluctuating antibody titres coexist with a high background of thyroid dysfunction, whereas in iodine-sufficient populations the association between obesity-related inflammation and TPOAb positivity is more evident, and iodine excess itself can precipitate thyroid autoimmunity in genetically susceptible individuals. Sex and reproductive status likewise modify the association, with a stronger inflammation-antibody link reported in women, particularly before menopause, whereas androgens and differences in fat distribution may attenuate the association in men (14). Thyroid functional status is another critical confounder: hypothyroid patients have elevated TSH that stimulates thyrocyte activity and antigen release, and thyroid hormones themselves influence inflammatory and metabolic indices, so analyses restricted to euthyroid individuals are more informative (12). Finally, because almost all available studies are cross-sectional, reverse causation cannot be excluded: obesity, insulin resistance and low-grade inflammation may be consequences rather than causes of thyroid autoimmunity, or both may arise from shared upstream determinants such as chronic stress, poor diet and physical inactivity. Only prospective designs with serial antibody and thyroid-function measurements can separate antibody initiation from progression to clinical disease.

The direction of the association is also required. Hypothyroidism may be caused by obesity, high-density lipoprotein cholesterol and inflammation in general, so there is reverse causation. Alternatively, there may be changes in systemic cytokines due to the disease itself. Only people with euthyroid function need to be tested at present, and we will follow up with them later; otherwise, the biochemical test may miss minor symptoms caused by subclinical hypothyroidism.

Pregnancy is a case with clinical information. TPOAb positivity is associated with postpartum thyroiditis and adverse thyroid conditions in some women, and pregnancy itself has significant changes in the immune system and metabolism (3, 27). It is still unknown whether the background SCLGI before conception can improve the prediction of TSH, free thyroxine, antibody status, iodine exposure and known obstetric risk factors. Older people are also in this category, and they have both inflammaging and more antibodies.

Mendelian randomisation (MR) studies, which use genetic instruments as proxies for lifelong

exposure, can help determine causality. Genetic instruments of body mass index, CRP, IL-6 signalling or immune traits may be involved in the development of thyroid autoimmunity due to inflammation, but pleiotropy and phenotypic definition are still problems. In the future, a positive test result for an incident autoantibody will be regarded as conclusive, and only then will any temporary or prolonged fluctuations in seropositivity and thyroid function need to be monitored again. However, MR findings depend on instrument strength and on the absence of horizontal pleiotropy, and current genetic studies of thyroid autoimmunity remain limited by phenotypic heterogeneity.

Biomarker Perspectives

Conventional inflammatory measures

HS-CRP is cheap, normalised and available in various parts. It is an acute-phase reaction in the liver mainly induced by IL-6, but is not specific to autoimmune diseases. Mild elevation may indicate a general increase in inflammation, especially with cardiometabolic diseases, but it can also be due to acute infection, smoking, obesity and drugs (28). Erythrocyte sedimentation rate has relatively low specificity and is influenced by age, sex, anaemia, etc. Neither marker should be used alone for the diagnosis of thyroid autoimmunity.

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio and systemic immune-inflammation index are all simple indicators based on complete blood counts and are easy to obtain. They have been studied together with AITD activity and thyroid disease, especially in GD. However, their ability to predict the first appearance of thyroid autoantibodies has not yet been verified, and preanalytic variations, infections, smoking, etc., in blood can interfere with the analysis results (29).

Cytokines, chemokines, and immune-cell phenotyping

IL-6, TNF- α , IL-1 β , IFN- γ , IL-17, IL-23, CXCL10, BAFF and soluble immune receptors are more directly involved in the pathways mentioned above. CXCL10 is of interest because it is induced by IFN- γ and participates in the recruitment of CXCR3-positive Th1 cells; increased levels have been described in autoimmune thyroid disease (30). Cytokine assays also have the problem of sample handling, circadian rhythms, different assay platforms and transient inflammation. A single time point may not show differences under the various conditions of the clinical environment.

Flow cytometry can be used to determine the frequency of Treg, Th17, T follicular helper (Tfh), memory B cells, plasmablasts, etc., in greater detail. However, there is no standardised gating strategy at present, and circulating cells are different from those in the tissue. Studies have found that several cytokines and changes in immune cell phenotype together have more predictive power than any one of them.

Metabolic, oxidative, and gut-related biomarkers

Adipokines, fasting insulin, homeostatic model assessment of insulin resistance, lipid indicators, uric acid, oxidative stress markers, etc., may be related to the metabolic basis of SCLGI. Whether they can provide predictive information will determine if they are included in the group of anthropometry and standard metabolic tests. Indicators of intestinal permeability, lipopolysaccharide-binding proteins, microbial metabolites and the composition of the stool microbiome are scientifically rich but have not reached the level of individual risk prediction based on methodology yet (8, 11, 12).

Comparative evaluation of candidate biomarkers

From a clinical practicability standpoint, the candidate markers differ substantially. hs-CRP and complete blood count-derived ratios (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, systemic immune-inflammation index) are inexpensive, automated, widely available and reproducible, but their specificity for thyroid autoimmunity is low and their predictive efficiency for incident TPOAb or TgAb positivity remains unproven (28, 29). Cytokine and chemokine panels (IL-6, TNF- α , IL-17, CXCL10, BAFF) are mechanistically closer to the SCLGI-AITD pathways and show promising association signals, but they are comparatively costly, sensitive to pre-analytical handling and circadian variation, and limited by inter-laboratory variability and the lack of standardized reference ranges (30). Immune-cell phenotyping by flow cytometry provides biologically detailed information but requires specialized laboratories, standardized gating strategies and fresh samples, and circulating immune cells only partly reflect intrathyroidal events (30). Metabolic markers (adipokines, insulin-resistance indices, uric acid, oxidative-stress markers) are accessible through routine biochemistry and relate directly to the metabolic drivers of SCLGI, yet their association with thyroid autoantibodies is weak and inconsistent and they are strongly influenced by thyroid hormone status itself (24). Gut-related biomarkers (lipopolysaccharide-binding protein,

SCFAs, microbiome composition) are scientifically novel but remain limited by methodological standardization and cost (31–34). Taken together, no single marker currently combines low cost, high accessibility, acceptable specificity and proven predictive efficiency for population screening; the most realistic strategy is a staged approach in which inexpensive first-line inflammatory and metabolic indicators identify at-risk individuals, followed by more expensive cytokine, immune-phenotyping or microbiome assays only in selected groups.

A reasonable biomarker model should have the following four levels: (i) Thyroid-specific susceptibility and early injury indicators, such as TSH, free thyroid hormone, TPOAb, TgAb and, if necessary, TRAb; (ii) Inflammatory load, which includes hs-CRP and a specific group of cytokines and chemokines; (iii) Metabolic background, such as waist circumference, glycaemic index, lipid profile, adipokines, etc.; and (iv) Host-modifying factors, such as age, sex, family history, iodine intake, smoking status, pregnancy status, genetic risk, etc. Calibration, discrimination, reclassification and clinical utility need to be used to test the prediction values; statistical association is not enough.

Challenges for clinical translation of composite biomarker panels

Although the four-level framework above is biologically attractive, several practical limitations must be acknowledged before it can be translated into clinical use. First, the measurement cost accumulates rapidly when cytokines, adipokines and multi-omics assays are combined with routine thyroid tests; hs-CRP and complete blood counts are inexpensive and universally available, whereas multiplex cytokine panels, flow-cytometric phenotyping and metabolomic or microbiome sequencing remain too expensive and time-consuming for population-level screening. Second, there is no standardized testing protocol: sample collection time, fasting status, centrifugation, storage temperature and freeze-thaw cycles all influence cytokine and adipokine concentrations, and different assay platforms (ELISA, chemiluminescence, bead-based multiplex) yield poorly comparable absolute values. Third, inter-laboratory variability of cytokine assays is substantial, often with coefficients of variation that exceed the thresholds accepted for clinical laboratory tests, and reference ranges differ across laboratories and populations. Fourth, most candidate markers are not specific to thyroid autoimmunity and are perturbed by acute infection, smoking, medications, pregnancy and circadian rhythms, so a composite score cannot yet discriminate SCLGI-related thyroid risk from other inflammatory states. Finally, the predictive performance of any composite panel must be formally tested through calibration,

discrimination and reclassification analyses in independent prospective cohorts before it can be recommended for risk stratification; the currently available evidence is, as emphasized throughout this review, largely cross-sectional.

Clinical and Research Implications

Currently, there is no data to support the idea that a broad inflammatory panel in the general population can predict thyroid autoantibodies. Thyroid antibody tests should be carried out under certain circumstances, such as when there are unknown thyroid disorders, in the selection process for different conditions (e.g., pre-pregnancy risk assessment, infertility investigation, goitre screening) as stipulated in the rules of the local medical department. In people with developed antibody positivity, it is still possible to assess thyroid function and clinical risk; otherwise, one would have to try to normalise non-specific biomarkers.

Nevertheless, a reduction in the inflammatory burden is also a good way of general prevention. Weight control, regular exercise, a good diet, sufficient sleep, quitting smoking, treating metabolic diseases, etc., can reduce cardiometabolic inflammation and improve the general state of health. These interventions should not be promoted as guaranteed ways to avoid AITD because there is no direct evidence that they can prevent the onset of antibodies or the development of disease. Selenium supplementation, iodine modification and immunomodulatory therapy need to be carried out with caution and should be personalised; too much iodine can exacerbate autoimmunity in vulnerable people (5). The clinical trial evidence for these strategies is, however, conflicting and population-dependent. For selenium, several randomized trials and meta-analyses in iodine-sufficient European populations reported that selenomethionine supplementation lowered TPOAb titres and improved thyroid ultrasound echogenicity, particularly in patients with higher baseline antibody levels (22, 35); other trials found no significant reduction in antibody titres or in progression to overt hypothyroidism, and the benefit was less consistent in iodine-deficient regions where selenium status and iodine supply interact (22, 35). In TPOAb-positive pregnant women, one randomized study suggested that selenium reduced the risk of postpartum thyroiditis and permanent hypothyroidism, although this finding has not been consistently replicated (36). For iodine, the relationship is U-shaped: correcting severe iodine deficiency reduces goitre and nodular thyroid disease, whereas iodine supplementation in mildly deficient or iodine-replete populations has been associated with increased thyroid autoimmunity, especially in genetically susceptible women (12, 37).

Vitamin D supplementation has been proposed as an immune-modulating strategy, but randomized data on TPOAb titres remain heterogeneous and largely inconclusive (38). Lifestyle-based anti-inflammatory interventions have not been tested in randomized trials with antibody seroconversion as the endpoint, so their benefit for AITD prevention remains hypothetical. Overall, the susceptible groups most likely to benefit from targeted anti-inflammatory interventions appear to be young TPOAb-positive women with a high inflammatory burden, individuals with coexisting metabolic syndrome, and patients in iodine-sufficient regions with marginal selenium status; universal selenium or iodine supplementation in unselected populations is not justified by the current evidence.

More research will be conducted in the future in the direction of prospect and highly phenotyped cohorts. Before the antibody test, check for any signs of inflammation and related indicators in the thyroid; note any recent infections or drug consumption, and then perform standard antibody tests. The site of the mechanobiological experiment should include thyroid tissue, draining lymph nodes (if available), peripheral blood, adipose tissue, gut-derived signals, etc. Genomics, epigenomics, proteomics, metabolomics and microbiome analysis, etc., have identified many different subgroups within SCLGI. Finally, it should be determined from the intervention trial whether reducing metabolic inflammation alters the course of antibodies and whether only the inflammatory indicators are affected.

Conclusion

SCLGI is a biologically reasonable reason for the formation of thyroid autoantibodies. Activation of the innate immune system, increased antigen presentation, oxidative stress, an imbalance in Th1/Th17-Treg cells and B-cell survival signals can prolong the inflammatory stage and lower the threshold for tolerance loss to thyroid disease. Obesity, insulin resistance, dysbiosis, aging and stress can all lead to the above conditions, but their extent and direction are not the same for everyone.

At present, the only evidence for this is associative; it cannot be concluded that SCLGI causes thyroid autoantibody seroconversion. Therefore, the inflammatory index should be combined with other risk factors in the general risk system rather than used on its own. In the future, a study will be carried out to observe the pre-clinical stage of immune susceptibility, the beginning of continuous antibody positivity and overt AITD. Therefore, the purpose of this paper is to put forward some targeted preventive measures and determine whether a reduction in the load of chronic inflammation can change the course of thyroid autoimmunity.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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