

Morphological Characteristics of the Thyroid Gland in Polypharmacy With Anti-Inflammatory Drugs

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Summary: Thyroid pathology is considered a marker of environmental distress. The most significant morphophysiological structure of the thyroid gland is the tissue microregion, which unites a group of follicles and the interfollicular space with an autonomous blood and lymph circulation system. It is precisely the structures of the tissue microregion that suffer the most from the action of pathogenic factors on the thyroid gland, reducing its role in ensuring morphological and metabolic changes in tissues and organs [Borodin Yu.I., et al., 2018]. However, the morphological and morphometric changes in the thyroid gland during polypharmacy with anti-inflammatory drugs have been poorly studied. The article presents a review of the literature on structural changes in the thyroid gland during polypharmacy with **anti-inflammatory drugs**.

Keywords: polypharmacy, thyroid gland, morphology, anti-inflammatory drugs.

Relevance

According to the World Health Organization (WHO), thyroid diseases rank second among endocrine disorders after diabetes. Statistics show that up to one-third of the world's population suffers from thyroid dysfunction. Over 740 million people worldwide have endemic goiter or suffer from other thyroid pathologies; 1.5 billion people are at risk of developing iodine deficiency diseases. At the same time, according to statistics, the increase in the number of thyroid diseases worldwide is 5% per year [N.Yu. Kryuchkova et al., 2018]. In recent decades, the functional state of the thyroid gland in patients of various profiles has been actively studied. It is known that thyroid hormones regulate the state of all organs and systems in the human body, primarily the processes of cell growth, maturation, and differentiation [A.R. Volkova, 2018]. Due to the growth of endocrine pathology worldwide, significant attention is being paid to the issues of thyroid morphology. Thyroid pathology ranks second after diabetes [O.V. Gorchakova, 2019]. Thyroid pathology is considered a marker of environmental distress. The most significant morphophysiological structure of the thyroid gland is the tissue microregion, which unites a group of follicles and the interfollicular space with an autonomous blood and lymph circulation system. It is precisely the structures of the tissue microregion that suffer the most from the action of pathogenic factors on the thyroid gland, reducing its role in ensuring morphological and metabolic changes in tissues and organs [Borodin Yu.I., et al., 2018]. In fact, the thyroid parenchyma is formed by a system of thyroid cells, among which two main types are distinguished - follicular and interfollicular cells. The first form follicles capable of extracellular accumulation of hormonally active substances. The latter participate in the proliferation of the thyroid parenchyma, forming interfollicular islands between the follicles. The morphogenetic potential of stromal-parenchymal relationships is determined by the ratio of follicular epithelial tissue, colloid, and interstitium. The significance of the thyroid gland (TG) for the body's vital activity is difficult to overestimate [Starkova I., 2012]. In addition to thyroid cells - the main cellular population that makes up the follicular compartment of the gland, it contains a second cellular group - calcitonin cells (parafollicular or C-cells) [Solyannikova D.R., Bryukhin G.V., 2009]. They have neurogenic origin and belong to the so-called APUD-system [Smirnova T.S., 2009], which is a cell population scattered in various organs and producing various biologically active substances, considered a diffuse neuroendocrine system [Sazonov V.F., 2014].

Parafollicular cells are located in small groups in the thyroid gland and/or lie on the basement membrane between thyrocytes (intraepithelially), but never border the follicle lumen. The maximum

number of them is concentrated in the central sections of each part of the thyroid gland, which is called the "C-cell region." Parafollicular cells make up no more than 1% of the thyroid epithelium. They are 2-3 times larger than thyroid cells, polygonal or slightly elongated in shape, have larger and light nuclei with 1-2 dense nuclei and a pale cytoplasm containing small argyrophil granules. The term "polypharmacy" (from poly - many and pragma - subject, thing) means the simultaneous and often unjustified appointment of a multitude of drugs or therapeutic procedures. Polypharmacy is nothing more than a pharmaceutical pressure on the patient as a result of irrational comprehensive approach. In outpatient and inpatient settings, patients are often prescribed more than two medications simultaneously. Moreover, the doctor does not always know what the patient is actually taking and in what doses, and discomfort often occurs. Polypharmacotherapy can occur not only due to a large number of co-morbidities and conditions in the patient, but also due to the incorrect choice of medications, when the patient takes unilateral, mutually exclusive or optional medications. There is insufficiency or distortion of the effect of the prescribed drug, caused by changes in metabolic processes in the elderly body. This often leads to incorrect correction of treatment tactics in the direction of increasing the number of medications or replacing them with stronger ones. The consequences of polypharmacy are a decrease/absence of treatment effects, adverse side effects, frequent hospitalizations, and high financial costs for both the patient and the healthcare system as a whole. The scientific medical community offers proven methods of combating polypharmacy in the form of various analytical algorithms for pharmacotherapy. These include the drug rationality index, Pearce's criteria, the STOPP/START, FORTA, and PINCER criteria. Unfortunately, the frequency and consequences of irrational polypharmacy in outpatient clinical institutions of our country remain insufficiently studied.

Thyroid diseases are one of the most common types of endocrine pathology, caused by many factors, among which particularly important are iodine deficiency, elevated radiation background, unfavorable environmental conditions, and psychoemotional stress. Acute and chronic stress can disrupt the secretion of thyroid hormones and significantly alter the morphology of the gland, causing changes of varying severity and direction. Drug exposure to the immune system often leads to the development of adverse events such as autoimmune diseases. Of all the organs of the endocrine system, the thyroid gland is most often affected, an organ whose features of embryonic development predispose to both spontaneous and induced lesions under various autoimmune influences. The term "polypharmacy" is often used in medical literature, but there is no universally accepted definition. In domestic literary sources, polypharmacy is defined as the simultaneous prescription of a large number of drugs, including their unjustified use. In foreign literature, the term "polypharmacy" (from Greek poly- and pharmacy - medicine) is used. In other literary sources, there is a qualitative definition of polypharmacy - prescribing more drugs to a patient than the clinical situation requires, and a quantitative definition - prescribing 5 or more drugs to a patient. The reason for the simultaneous prescription of several drugs may be the presence of concomitant diseases (multimorbidity), drug availability, as well as clinical recommendations, guidelines of professional medical societies, treatment standards, which in some cases contain recommendations for the use of complex therapy with more than 5 drugs only for one indication, the effectiveness of which corresponds to a high level of evidence. Analysis of the literature shows that today, combating polypharmacy with anti-inflammatory drugs is one of the important tasks of providing medical care to patients of all ages. This highlights the need to develop strategies that improve the quality of medical care and reduce side effects to medications.

At the end of the 20th century, P.J. Davis and co-authors discovered and subsequently studied non-genomic mechanisms of action of thyroid hormones (TH), which are initiated by plasma membrane receptors for T3 and T4, located on the integrin $\alpha V\beta 3$. This integrin is expressed on the surface of leukocytes, platelets, and epithelial and endothelial cells, facilitating interaction between cells, as well as between leukocytes and biological surfaces. Non-genomic mechanisms include TH stimulation without the involvement of gene transcription for mitogen-activated protein kinase, phosphatidylinositol-3-kinase, and serine-threonine kinase, thereby promoting tumor progression:

angiogenesis, cell proliferation, and cell migration. Additionally, iodothyronines, in a dose-dependent manner, can stimulate the expression of tissue-specific pro-inflammatory genes, thus providing systemic pro-inflammatory action, which leads to an immunopathological process at the tissue and organ levels. Given the systemic pro-inflammatory effect of TH, it is hypothesized that prolonged hyperthyroidism may contribute to the development of a chronic inflammatory reaction that makes cells more susceptible to malignancy. Cytokine-induced thyroiditis (occurring as a destructive variant in 50-70% of cases) and thyroid damage during the use of immune checkpoint inhibitors are well-known (the use of a combined treatment regimen CTLA-4 + PD-1/PD-L1 leads to an increase in the frequency of hypothyroidism up to 20%). Some researchers observe effects on immune processes even in iatrogenic thyroid disorders such as lithium-induced gland dysfunction. The authors describing these lesions note that the predisposition to autoimmune thyroid lesions or the nature of the disease being treated (lithium in bipolar affective disorder; interferon α in hepatitis C) also have autoimmune mechanisms at their core. Conclusion: From the above literature review, it becomes clear that research on polypharmacy and its impact on the endocrine system, especially the thyroid gland, is insufficient. Among the available data, there are some discrepancies that require further morphological and morphometric studies.

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