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AGE AND SEX - RELATED MORPHOFUNCTIONAL CHANGES OF THE THYMUS AND THEIR IMPACT ON THE IMMUNE SYSTEM

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Abstract. The thymus is the primary immune organ responsible for generating self-tolerant and production of immunocompetent T cells and, with aging, sex, it atrophies & declines in functions. *Age-Related Morphofunctional Changes* :(*Age* : natal, postnatal, adult, and old). *Age-related thymic involution* is the progressive Structural break-down, Degeneration, Cellular Loss and Reduced Output of the Thymus. Thymic involution has many negative impacts on immune function including reduced pathogen resistance, Reduced T-Cell Diversity during Cancer development, High chance of Auto-immunity activities.The compromised thymic microenvironment in aged individuals substantially disturbs thymocyte development and differentiation. Growth factors, cytokines, transcription factors, micro RNAs regulates Thymic Age-related involution. Sex-Related Morphofunctional Changes : The thymus undergoes thymic involution—the replacement of functional tissue with fat—at different rates and through distinct structural patterns based on biological sex. Involution Kinetics, Hormonal Regulation of Epithelial Cells (TECs), Structural Dimorphism: Women & Men. Impact on the Immune System : Naïve T-Cell Depletion, Impaired Defense, Autoimmunity and Inflammation.

Keywords: Thymus, age-related involution, sex differences, morphofunctional changes, naïve T cells, autoimmunity, immune system, cytokines, microRNA.

Аннотация. Тимус является основным органом иммунной системы, ответственным за формирование иммунокомпетентных и самотолерантных Т-лимфоцитов. С возрастом и в зависимости от пола происходит его атрофия и снижение функциональной активности. **Возрастные морфофункциональные изменения** (неонатальный, постнатальный, взрослый и пожилой периоды) характеризуются прогрессирующей возрастной инволюцией тимуса, которая включает структурную деградацию, дегенерацию, потерю клеток и снижение продукции Т-клеток. Возрастная инволюция тимуса приводит к снижению устойчивости к инфекционным агентам, уменьшению разнообразия Т-клеточного репертуара в процессе канцерогенеза, а также к повышенному риску развития аутоиммунных реакций. Нарушение микросреды тимуса у пожилых лиц существенно влияет на развитие и дифференцировку тимоцитов. Ростовые факторы, цитокины, транскрипционные факторы и микроРНК участвуют в регуляции возрастной инволюции тимуса. **Половые морфофункциональные изменения** характеризуются различиями в скорости и структурных особенностях инволюции тимуса. У мужчин и женщин отмечаются различия в кинетике инволюции, гормональной регуляции тимусных эпителиальных клеток (ТЭК) и структурном диморфизме тимуса. **Влияние на иммунную систему** проявляется истощением наивных Т-клеток,

снижением защитных иммунных реакций, развитием аутоиммунных процессов и хронического воспаления.

Ключевые слова: Тимус, возрастная инволюция, половые различия, морфофункциональные изменения, наивные Т-клетки, аутоиммунитет, иммунная система, цитокины, микроРНК.

Annotatsiya. Timus immun tizimining asosiy organi bo‘lib, immunokompetent va o‘ziga tolerant T-limfotsitlarning shakllanishini ta’minlaydi. Yosh va jins omillariga bog‘liq holda timusda atrofiyalanish va funksional faollikning pasayishi kuzatiladi. **Yoshga bog‘liq morfofunksional o‘zgarishlar** (neonatal, postnatal, voyaga yetgan va keksalik davrlari) timusning progressiv involyutsiyasi bilan tavsiflanadi. Bu jarayon strukturaviy yemirilish, degeneratsiya, hujayralar yo‘qolishi va T-hujayralar ishlab chiqarilishining kamayishi bilan kechadi. Timus involyutsiyasi infeksiyalarga qarshi rezistentlikning pasayishi, saraton rivojlanishida T-hujayra xilma-xilligining kamayishi hamda autoimmun kasalliklar xavfining oshishiga olib keladi. Keksalarda timus mikro muhitining buzilishi timozitlarning rivojlanishi va differensiyatsiyasini izdan chiqaradi. O‘sish omillari, sitokinlar, transkripsion omillar va mikroRNKlar timus involyutsiyasining boshqarilishida muhim rol o‘ynaydi. **Jinsga bog‘liq morfofunksional o‘zgarishlar** erkak va ayollarda timus involyutsiyasining tezligi, timus epitelial hujayralarining (TEH) gormonal regulyatsiyasi hamda strukturaviy dimorfizmi bilan farqlanadi. **Immun tizimiga ta’siri** naiv T-hujayralarning kamayishi, himoya reaksiyalarining sustlashuvi, autoimmun jarayonlar va surunkali yallig‘lanish rivojlanishi bilan namoyon bo‘ladi.

Kalit so‘zlar: Timus, yoshga bog‘liq involyutsiya, jinsiy farqlar, morfofunksional o‘zgarishlar, naiv T-hujayralar, autoimmunitet, immun tizimi, sitokinlar, mikroRNK.

Introduction

The thymus is primary immune organ, located in the anterior mediastinum. It is made up of two lobes that meet in the upper midline, and stretch from below the thyroid in the neck to as low as the cartilage of the fourth rib.The lobes are covered by a capsule.The thymus lies behind the sternum, rests on the pericardium, and is separated from the aortic arch and great vessels by a layer of fascia. The left brachiocephalic vein may even be embedded within the thymus. In the neck, it lies on the front and sides of the trachea, behind the sternohyoid and sternothyroid muscles.

The thymus consists of two lobes, merged in the middle, surrounded by a capsule that extends with blood vessels into the interior. The lobes consist of an outer cortex rich with cells and an inner less dense medulla. The lobes are divided into smaller lobules 0.5-2 mm diameter, between which extrude radiating insertions from the capsule along septa. The cortex is mainly made up of thymocytes and epithelial cells.The thymocytes, immature T cells, are supported by a network of the finely-branched epithelial reticular cells, which is continuous with a similar network in the medulla. This network forms an adventitia to the blood vessels, which enter the cortex via septa near the junction with the medulla. Other cells are also present in the thymus, including macrophages, dendritic cells, and a small amount of B cells, neutrophils and eosinophils. In the medulla, the network of epithelial cells is coarser than in the cortex, and the lymphoid cells are relatively fewer in number. Concentric, nest-like bodies called Hassall's corpuscles (also called thymic corpuscles) are formed by aggregations of the medullary epithelial cells. These are concentric, layered whorls of epithelial cells that increase in number throughout life. They are the remains of the epithelial tubes, which grow out from the third pharyngeal pouches of the embryo to form the thymus.

Age- related Morphofunctional changes of the Thymus : Thymic function gradually starts to decrease from the first year of life. With age there is an expansion of the perivascular space and a simultaneous Degeneration of the thymic epithelial space. The lymphoid component within the Thymic Epithelial Space; Cortex and Medulla begins to involute shortly after birth and decreased by 3% per year through middle age from 35–45 years of age and 1% per year throughout the rest of life. Involution of the Thymic Epithelial Space and expansion of the perivascular space; adipocytes,

peripheral lymphocytes, stroma with age alters the Thymic Epithelial Space to PVS ratio and leads to the TES becoming <10% of the total thymus tissue by age 70 years. Reduction of TES and functional thymopoiesis, with aging, subsequently results in loss of TCR gene rearrangement and decreased output of naïve T cells to the periphery. Using single joint T cell receptor excision circle analysis (sjTREC), a molecular marker for active thymopoiesis, we and others have reported a steady three-log decline in circulating naïve T cells across an 80 year lifespan. Thus thymic involution with age results in diminished thymopoiesis, i.e. decreased quantity and quality of T cells exported across the lifespan.

Male morphofunctional changes of the thymus and their impact on the immune system. In males, the thymus undergoes profound morphofunctional changes—primarily a process called age-related thymic involution—that serves as a primary driver of immune system senescence. This regression is significantly accelerated in males compared to females, largely due to the influence of androgens like testosterone.

Morphological Changes. The male thymus begins to shrink as early as the first year of life, with a peak rate of atrophy starting at puberty. Tissue Atrophy: Functional thymic parenchyma is gradually replaced by adipose (fat) tissue and fibrous cells. In humans, thymic epithelial space can decline to less than 10% by age 70. Structural Disorganization: The distinct boundary between the cortex and medulla (the cortico-medullary junction) is lost. Cortical thymic epithelial cells (cTECs), which have extensive network projections in youth, contract and decrease in number. Cellular Loss: There is a significant reduction in total thymic cellularity, specifically affecting early T-lineage progenitors (ETPs) and double-positive (CD4+CD8+) thymocytes.

Functional Changes & Hormonal Influence. The "thymic clock" in males is uniquely set by sex hormones: Androgen-Mediated Involution: Testosterone acts directly on androgen receptors in thymic epithelial cells (TECs), repressing essential genes like Foxn1 and Dll4 which are required for T-cell development. Local Glucocorticoid Synthesis: Testosterone triggers the synthesis of glucocorticoids within the thymus itself, which induces apoptosis (programmed cell death) in developing thymocytes.Transient Reversibility: Surgical or chemical castration (sex steroid ablation) can transiently reverse this atrophy, leading to a "rebound" in thymus size and T-cell production.

Impact on the Immune System. These morphological shifts lead to a condition known as immunosenescence, characterized by: Reduced Naïve T-Cell Output: The primary consequence is a drastic decline in the production of new, "naïve" T-cells capable of recognizing new pathogens or vaccines. Shift to Memory T-Cells: To compensate for low output, the body relies on homeostatic proliferation of existing T-cells. This results in a "memory-heavy" immune system with a restricted T-cell receptor (TCR) repertoire, creating "holes" in immune coverage. Increased Disease Susceptibility:Infections: Higher vulnerability to viruses like influenza and West Nile Virus. Cancer: Attenuated tumor immunosurveillance increases cancer incidence in aging males. Autoimmunity: Paradoxically, thymic atrophy can impair negative selection (the removal of self-reactive cells), leading to an increased risk of autoimmune disorders. Chronic Inflammation ("Inflammaging"): The accumulation of senescent T-cells and dysregulated CD4+ subsets (such as cytotoxic CD4 T-cells) promotes a state of less -grade chronic systemic inflammation.

Female morphofunctional changes of the thymus and their impact on the immune system. In females, the thymus undergoes distinct morphofunctional changes influenced by unique physiological states—menstrual cycles, pregnancy, and menopause—resulting in a process of involution that is markedly slower and more resilient than in males.

Morphological Changes. While females experience age-related thymic atrophy, the process is delayed by roughly 10 to 20 years compared to males. Slower Adipose Replacement: Females exhibit significantly less fatty degeneration of the thymus between the ages of 40 and 69. Cortical Resilience: The female thymic cortex is proportionally larger and contains a higher number of double-positive (DP) thymocytes and cortical thymic epithelial cells (cTECs) than that of age-matched males. Organizational Shifts: Aging in women leads to a gradual loss of the clear cortical-

medullary boundary and a disorganization of perivascular spaces, though these changes are less pronounced than in men. Biphasic Pattern: Cortical degeneration in females follows a unique biphasic pattern, featuring a period of transient hypertrophy around age 42, followed by accelerated senile degeneration later in life.

Functional & Hormonal Dynamics. The female thymus is highly sensitive to fluctuating sex hormones, which dictate its functional state: Estrogen-Driven Involution: Elevated estrogen levels can inhibit the production of early thymic progenitors (ETPs) in the bone marrow and lead to a reduction in DP thymocytes. Pregnancy-Induced Atrophy: During pregnancy, the thymus undergoes acute, temporary involution driven primarily by progesterone. This includes a shrinkage of the cortex and a depletion of T-cell subsets to prevent the mother's immune system from rejecting the fetus. Post-Menopausal Rebound: The decline of estrogen after menopause can lead to a period of thymic hypertrophy and increased cortical area, as the inhibitory effect of estrogen is removed. Menstrual Fluctuations: During the follicular phase of the menstrual cycle, the regulatory T-cell (Treg) population in the thymus expands, peaking prior to ovulation before decreasing in the luteal phase.

Impact on the Immune System. These changes contribute to a sexual dimorphism in immunity, where women generally maintain more robust thymic output for longer durations: Prolonged Naïve T-Cell Output: Females maintain higher levels of recent thymic emigrants (RTEs) into their 50s and 1 minute contributing to a generally stronger immune response to infections and vaccines.

Autoimmune Vulnerability: Paradoxically, the slower rate of involution is linked to a higher susceptibility to autoimmune diseases (e.g., SLE, RA). This is attributed to lower expression of the AIRE gene (Autoimmune Regulator) in the female thymus, which can impair the negative selection of self-reactive T-cells. Maternal-Fetal Tolerance: Pregnancy-induced thymic changes promote the development of specialized Tregs that migrate to the placenta to ensure fetal tolerance while maintaining the mother's defense against infections. Extended Life Expectancy: Better sustained thymic function in females is considered a potential contributing factor to their generally longer life expectancy compared to males.

Summary: Age- and Sex-Related Morphofunctional Changes in the Thymus and Their Impact on the Immune System. The thymus is a primary lymphoid organ that plays a crucial role in the development, maturation, and selection of T-lymphocytes, which are essential for cell-mediated immunity. Its structure and function undergo significant changes with age and are also influenced by sex hormones, leading to measurable effects on immune competence. During early life, the thymus is relatively large and highly active. It contains dense lymphoid tissue with a well-defined cortex and medulla, providing an optimal microenvironment for T-cell differentiation and positive and negative selection. This high thymic activity ensures a robust and diverse T-cell repertoire, which is essential for effective immune responses in childhood. With advancing age, the thymus undergoes a process known as thymic involution. This is characterized by a gradual reduction in thymic size and weight, replacement of functional lymphoid tissue with adipose tissue, and blurring of the corticomedullary distinction. Functionally, thymic epithelial cells decline, thymic hormone secretion decreases, and the output of naïve T-cells is reduced. As a result, the immune system becomes less adaptable, leading to increased susceptibility to infections, reduced vaccine responses, higher incidence of autoimmune disorders, and increased cancer risk in the elderly. Sex-related differences in thymic morphology and function are largely mediated by sex hormones. Androgens and estrogens accelerate thymic involution, particularly after puberty. Males generally show earlier and more pronounced thymic atrophy compared to females. Females tend to retain thymic function for a longer period, which partly explains their relatively stronger immune responses but also their higher predisposition to autoimmune diseases. Overall, age- and sex-related morphofunctional changes in the thymus significantly influence immune system efficiency. Thymic involution leads to immunosenescence, while hormonal differences contribute to variations in immune responses between males and females. Understanding these changes is important for

improving immunization strategies, managing age-related immune decline, and developing therapies targeting immune modulation.

Literature review

Sexual Dimorphism in Involution: Recent 2025 and 2026 studies published in journals like MDPI International Journal of Molecular Sciences confirm that the female thymus remains structurally more resilient than the male thymus, experiencing delayed fatty replacement (steatosis) by roughly 10 to 20 years. Androgen-Mediated Mechanisms: Research published in Frontiers in Immunology (2022) and Endocrinology identifies that androgen receptors (AR) on thymic epithelial cells are the primary mediators of male-specific atrophy. Androgens suppress the expression of Foxn1, a transcription factor critical for T-cell development. Biphasic Atrophy in Females: Studies from 2023 and 2025 highlight a "biphasic" pattern of atrophy in women, characterized by a unique transient hypertrophy phase between ages 40–59, linked to fluctuating estrogen levels prior to menopause. T-Cell Output (sjTREC Levels): Findings regarding higher naïve T-cell output in females are based on sjTREC (signal joint T-cell receptor excision circle) quantification, which serves as a molecular marker for new T-cells. Large-scale studies show females maintain significantly higher sjTREC levels well into middle age compared to males. Autoimmunity and AIRE Gene: The paradox of slower female involution and higher autoimmune risk is supported by evidence that female sex hormones can decrease the expression of the AIRE (Autoimmune Regulator) gene in the thymus, which is essential for "negative selection" (the removal of self-attacking T-cells). Recent 2025/2026 Immunosenescence Research: Current articles from iScience (2025) and Nature Communications (2025) provide data on "inflammaging" patterns, showing that males exhibit an earlier shift toward memory T-cell dominance and inflammatory profiles compared to females.

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