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Region-Dependent Dynamics of Visceral Lymph Nodes Aging

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ABSTRACT

Aging alters the structure and function of many organs, including peripheral lymphoid organs. The operability of lymph nodes is determined by the unity of three functional systems: lymphoid tissue (compartments), water saturation and trace element balance. The change in each system is reflected in the morphofunctional status of the lymph node. These changes are region-dependent. Lymph nodes are indicators of age-dependent changes in the drained lymphatic region. This is confirmed by histological, thermogravimetric methods, X-ray fluorescence analysis using synchrotron radiation and statistical evaluation of dynamic rows. A difference has been established between visceral lymph nodes draining regions of the respiratory system and gastrointestinal tract. There is a different intensity of changes in basic indicators when evaluating structure (compartments), hydration, and trace elements. There is a different rate of age-induced changes in lymph nodes of different localization. Rapid aging is observed in the mesenteric lymph node, slow aging is noted in the tracheobronchial lymph node. Basic indicators and total growth coefficient are proof of different rates of lymph nodes aging. The implementation of the regional principle of aging for lymph nodes is obvious.

INTRODUCTION

Aging affects all organs and systems of the body without excluding peripheral lymphoid organs [1-3]. Lymph nodes play a priority role in protecting and ensuring endoecological safety, especially in retirement age. Lymph nodes have certain localization. Different location of lymph nodes is the reason for creating the concept of lymphatic region [4]. We expect lymph nodes to have individual differences in aging. This is due to the features of the drained lymphatic region. Lymphatic regions of the respiratory system and digestive organs are very different due to the performance of certain functions and features of contact with the external environment. Destabilization of the structure and function of the lymphatic system and organs is a sign of age pathology [1]. Changes in organs depend directly on the state of the lymph system and on the operability of a lymph node. Processes of involution in lymph nodes make it difficult to drain extracellular space and reduce immune protection in lymphatic region [5-7].

Lymph node is considered as marker of state of drained lymphatic region [1,2,8]. Morphophysiological basic indicators can be used to characterize senile lymph node transformation. The lymph node is a triune homeostatic system. This functional system consists of structure (lymphoid), hydration and trace elements. These components allow to maintain operability of lymph nodes in different periods of life [4,9]. Lack of knowledge about each functional system does not allow to understand the role of the lymph node in the pathogenesis of aging. Only integration of knowledge about each functional system will allow to assess age dynamics of visceral lymph nodes depending on territorial affiliation to respiratory organs and gastrointestinal tract. The primary purpose of the study is to assess the intensity of age changes in visceral lymph nodes depending on the lymphatic region.

MATERIAL AND METHODS

The experiment was performed on 160 white Wistar rats with conditional age division into young (3-5 months) and old (18-20 months). Each age corresponds to the basic and final periods of the study. Work with animals was carried out in accordance with international standards (Directives of the Council of the European Communities of 24 November 1986, 86/609/EEC) and Order of the Ministry of Health of Russia No. 267 of 19.06.2003. Animals received a standard diet with free access to water.

Mesenteric and tracheobronchial lymph nodes were chosen as the object. The following methods are used: 1) histological method with morphometry of morphofunctional zones of lymph nodes stained with hematoxylin and eosine; 2) thermogravimetric method with determination of total water and free and bound fractions of water in lymph nodes [10]; 3) X-ray fluorescence analysis using synchrotron radiation (RFA SI) to determine trace elements (Mn, Fe, Cu, Zn, Se) in lymph nodes on equipment of the G.I. Budker's Institute of Nuclear Physics [11]; 4) StatPlus Pro 2009, AnalystSoft Inc to determine arithmetical mean (M), standard error of the mean (± m), difference confidence at $p < 0.05$; 5) statistical analysis of dynamic rows of data of initial (basic) and final periods with determination of the following indicators: absolute increase or decrease (Δy) – as difference between two levels of series; growth coefficient (Cg) – as the ratio of the finite row to the initial row; growth rate ($Rg\%$) is nothing more than growth coefficient in percent (coefficient is multiplied by 100); increase rate (Ri) is defined as subtraction of 100 from the growth rate or subtraction of 1 from the growth coefficient. We compare the base period (initial level, y_o) and the final row (y_i) of dynamics.

$$\Delta y = yi - yo \quad (1)$$

$$Cg = \frac{yi}{yo} \quad (2)$$

$$Rg = Cg \times 100\% \quad (3)$$

$$Ri = Rg - 100 \text{ или } Ri = Cg - 1 \quad (4)$$

RESULTS

The operability of the lymph node is ensured by three functional systems: lymphoid tissue (compartments), water saturation and trace elements [4,9]. Changing each of these systems in the lymph node affects its morphotype and functionality at different periods of life. The interaction of these systems affects the speed and intensity of lymph node aging. It is important to assess the intensity of lymph node change depending on territorial affiliation, as lymph nodes are indicators of the drained area [4].

Mesenteric lymph node

The mesenteric lymph node refers to the lymphatic region of the intestine. The lymph node contacts the external environment through the lumen of the gastrointestinal tract. The structure of mesenteric lymph nodes changes with age. Morphometric indicators of structural and functional zones and cellular composition confirm senile transformation of a lymph node [3,4]. Aging of the lymph node occurs at a certain rate to the age of animals 18-20 months.

We identified indicators for the final results of all changes in lymph node structures from baseline (Figure 1). The size of the compartments has different dynamics. Analysis of absolute increase or decrease (Δy) revealed two opposite trends compared to the initial (basic) period (Figure 1).

First, a negative value of the indicators indicates an absolute decrease (regression) in lymph node structures – cortical plateau, lymphoid follicles, paracortex, and lymphatic sinuses. Second, positive absolute increase values indicate capsule thickening (sclerosis), expansion of medullary cord in the medullary substance of the mesenteric lymph node when aging.

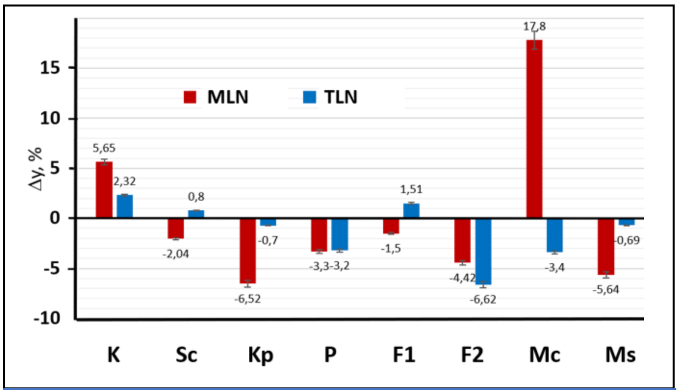

Figure 1: Absolute increase (or decrease) structures of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging. K: Capsule; Sc: Subcapsular Sinus; Cp: Cortical Plateau; P: Paracortex; F1: Lymphoid Follicle without a germinative center; F2: Lymphoid Follicle with a germinative center; Mc: Medullary Cords; Ms: Medullary Lymphatic Sinus.

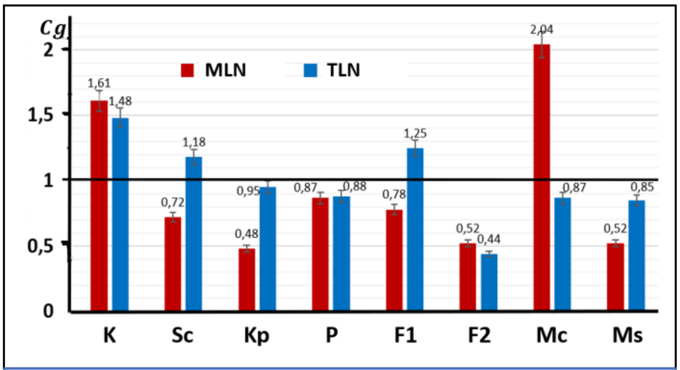

Figure 2: Growth coefficient for structures of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging. K: Capsule; Sc: Subcapsular Sinus; Cp: Cortical Plateau; P: Paracortex; F1: Lymphoid Follicle without a germinative center; F2: Lymphoid Follicle with a germinative center; Mc: Medullary Cords; Ms: Medullary Lymphatic Sinus.

Each of the lymph node structures is characterized by different dynamics intensity, judging by the growth coefficient (Figure 2). The growth coefficient shows how many times the size of the capsule and medullary cords was increased, but the size of other compartments decreased relative to the basic level. The increase rate was 105% for medullary cords and 61% for the capsule. Other lymph node structures showed a decrease the increase rate for subcapsular and medullary sinuses (28% and 48%, respectively), cortical plateau (52%), lymphoid follicles with and without germinative center (48% and 22%, respectively). There is a different intensity of change in morphofunctional zones of mesenteric lymph nodes when aging. Ubiquitous regression of cortical structures and narrowing of lymphatic sinuses leads to reduction of proliferative processes, drainage function and immune potential of lymph nodes in aging [3-5].

Age-induced change of lymph nodes requires certain aqueous saturation of lymphoid tissue [10]. Fluid deficiency progresses with age. There is an absolute decrease in total water and its free fraction with a slight increase in the volume of the bound water fraction (Figure 3). The dehydration intensity reflects the growth coefficient (Figure 4). The rate of water volume reduction is 33% for total water and 49% for free water fraction. This is largely the case for the free water fraction. Free water is the lymph of sinuses in the lymph node. There is a definite link between the size of lymphatic sinuses and the volume of free water. Narrowing of lymph sinuses reduces the volume of free-flowing lymph and indicates a decrease in drainage through the lymph node. The bound fraction of water has a slight absolute increase. The increase rate is 9% for the bound fraction of water in the cell-fibrous part of the lymph node. A bound fraction of water is necessary to maintain lymphoid cell proliferation in the aging organism.

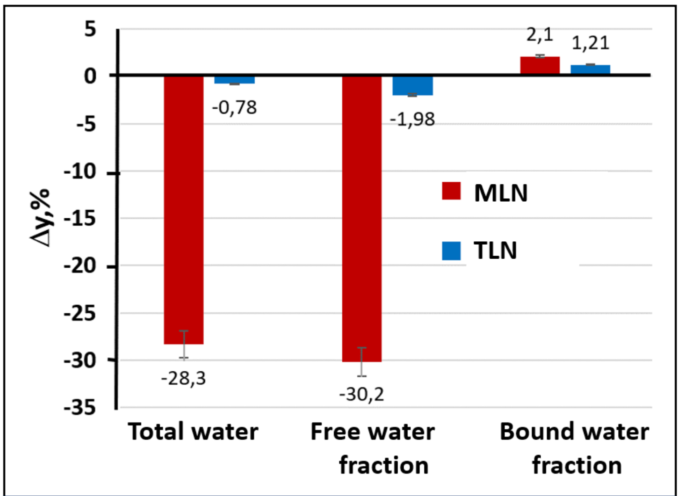

Figure 3: Absolute increase (or decrease) of total water, free and bound fraction of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging.

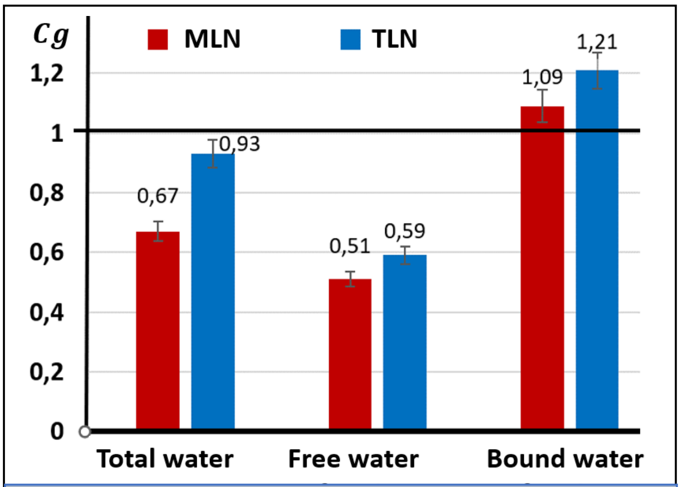

Figure 4: Growth coefficient for total water, free and bound water fractions of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging.

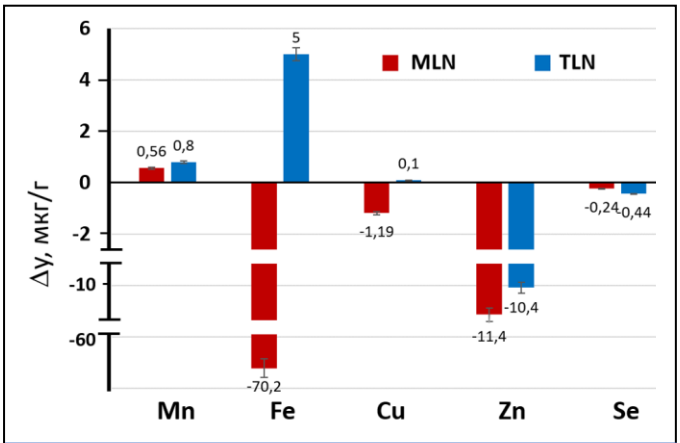

Figure 5: Absolute increase (or decrease) of trace elements concentration of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging.

Aging alters the trace elements profile of lymph nodes. Trace elements are a functional system of the lymph node. The proliferation of lymphoid cells and the dimension of lymph node compartments depend on the trace elements. We noted that the absolute indicator showing the difference between the basic and final dynamic rows for most trace elements has a negative value (Figure 5). There is a progressive decrease in concentrations of iron, zinc, copper and selenium. The absolute increase is positive only for manganese. The growth coefficient shows how many times the trace elements concentration changed when aging compared to baseline (Figure 6). The increase rate lags behind the base level, being 17%–18% for copper, zinc, selenium and 30% for iron. This indicates a deficiency of these trace elements. At the same time, manganese concentration increased by 26% of the base level. Senile imbalance of trace elements affects regulation of lymphoid cell proliferation and differentiation processes and compartment formation. Cells activity is directly related to enzymes and trace element concentration [12-15].

Thus, the mesenteric lymph node undergoes senile changes, the intensity of which is associated with low indicators for most structures (compartments) when expanding the medullary substance, the degree of water saturation, and the concentration of trace elements. Changing these components of lymph nodes is a destabilizing moment of adaptation-compensatory processes in peripheral lymphoid organs in senile age. Reduced drainage and immune functions of the lymph node increase the risk of polymorbid state in aging.

Tracheobronchial lymph node

The tracheobronchial lymph node refers to the bronchopulmonary region in contact with the air environment. Features of respiratory system operation determine morphophysiology of tracheobronchial lymph nodes. In aging, lymph nodes are reorganized by the end of the study (rat age is 18–20 months). There is a change in the basic indicators of lymph node structures.

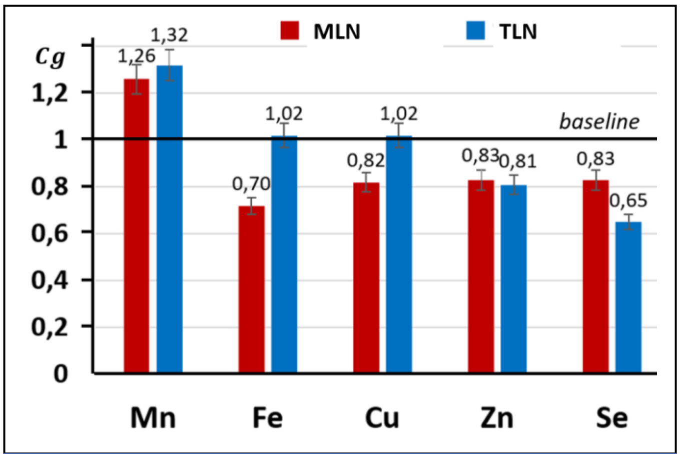

Figure 6: Growth coefficient of trace elements concentration of Mesenteric (MLN) and Tracheobronchial (TLN) lymph nodes in aging.

The absolute increase (or decrease) score revealed a difference between the orientation of changes in the size of lymph node structures in aging (Figure 1). This is confirmed by the presence of a negative or positive sign at the indicator. Regression is noted from the cortical plateau, paracortical area, lymphoid follicles with a germinative center, medullary substances structures (medullary cords and medullary lymphatic sinus). A positive absolute increase is observed from the connective capsule, subcapsular sinus, lymphoid follicles without a germinative center.

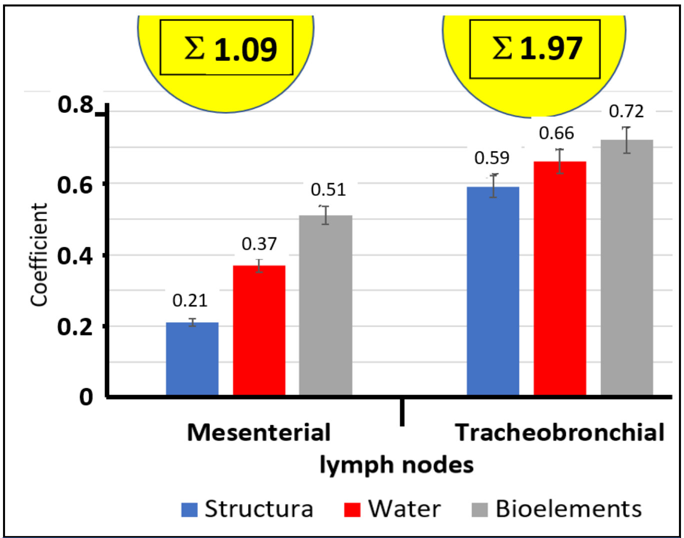

Figure 7: Total growth coefficient for structure, hydration and trace elements in mesenteric and tracheobronchial lymph nodes in aging.

The growth coefficient characterizes the ratio of the final to initial rows of lymph node structures (Figure 2). This coefficient shows how many times the lymph node structures have changed in the dynamics of the study. A growth coefficient greater than one indicates an intense increase in structures such as the capsule, subcapsular sinus, and lymphoid follicle without a germinative center in older animals. The increase rate was within the limits of 18%–48%, the highest indicator giving a connective capsule. The growth coefficient less than one indicates the intensity of reduction of other lymph node structures (cortical plateau, paracortex, lymphoid follicles with a germinative center, medullary cords, medullary sinus). The rate of increase (decrease) was 12%–15% for most structures of lymph nodes. The rate of decrease was only 5% for the cortical plateau and at most 56% for lymphoid follicles with a germinative center. There is a small degree of lymphoid tissue involution in the tracheobronchial lymph node. The degree of reduction of most lymph node structures is close to the baseline. The exception is lymphoid nodes with a germinative center. In aging, there is a decrease in proliferative processes, immune potential and drainage function of lymph nodes [4, 6].

The structure of tracheobronchial lymph nodes is characterized by a certain water saturation during different periods of life. The volume of fluid in the lymph node is limited due to its compact morphotype. The cortical substance dominates the lymph node. With age, there is a slight absolute decrease in the total amount of water and its free fraction and an increase in the bound water fraction from baseline (Figure 3). The intensity of the water saturation change is confirmed in the magnitude of the growth coefficient (Figure 4). The growth rate indicates the deficiency development of total water (7%) and free water fraction (41%). This is due to a real decrease of sinus system in the lymph node. The fraction of bound water retains a slight absolute increase, the increase rate was 21%. Such aqueous saturation is important for the functional activity of lymphoid cells in the aging organism [2,10].

A certain trace element profile reflects the morphofunctional status of the tracheobronchial lymph node at different periods of life. Age change of compartments integrates concentration of trace elements [9]. The trace elements of the immune group affect the proliferation processes of lymphoid cells and their distribution in structural and functional zones of the lymph node. An absolute increase is typical of manganese, iron, copper. An absolute decrease is typical of zinc and selenium with a slight deviation from baseline (Figure 5). The growth coefficient reflects a similar pattern (Figure 6). The increase rate is 32% for manganese, the increase rate does not change for iron and copper, the rate decreases zinc (19%) and selenium (35%). Obviously, the trace element profile is formed with zinc and selenium deficiency in aging. Trace element deficiency affects the structural organization of the tracheobronchial lymph node. Trace elements are part of enzymes. Enzymes regulate lymphoid cell proliferation processes and compartment sizes. Lack of trace elements and enzymes leads to destabilization of lymph node structure [4,9,12-15].

Comparative analysis of mesenteric and tracheobronchial lymph nodes

Lymphatic regions of the respiratory system and gastrointestinal tract differ from each other in their morphophysiological parameters. Age-dependent changes manifest differently in the mesenteric and tracheobronchial lymph nodes. Thus, connective tissue growth occurs more in the mesenteric lymph node than in the tracheobronchial lymph node. This is most noticeable in the thickness of the lymph node capsule. The opposite effect of size change is noted on the side of subcapsular sinus, lymphoid follicles without germinative center, medullary cords. These structures decrease in the mesenteric lymph node and increase in the tracheobronchial lymph node (Figure 1-2). There is the greatest intensity of change in cortical plateau size, medullary lymphatic sinuses noted in the mesenteric lymph node compared to the tracheobronchial lymph node. The reactivity of lymphoid follicles with a germinative center is reduced more in the tracheobronchial lymph node (Figure 2). The dimensions of the paracortical area are almost the same in both lymph nodes. The difference in the change in lymph node compartments indicates a regional specificity of aging.

Lymph node structure transformations determine dehydration intensity (Figure 3,4) Dehydration manifests itself most in the mesenteric lymph node. There is a decrease in total water and its free fraction. The tracheobronchial lymph node reacts by reducing a predominantly free fraction of water. The indicator is comparable to the mesenteric lymph node. Obviously, this is directly related to the reduction of the sinus system in aging.

The trace element profile differs in mesenteric and tracheobronchial lymph nodes (Figure 5,6). Aging results in an increase in manganese concentration in both lymph nodes. Iron and copper concentrations decrease in the mesenteric lymph node and remain at baseline in the tracheobronchial lymph node. Zinc and selenium trace elements are deficient in both lymph nodes. Selenium is greater deficiency in the tracheobronchial lymph node.

Three components of the lymph node (structure (compartments), aqueous saturation and trace element concentration) allow assessing the individual and overall operability of the lymph node. We calculated the total coefficient for each functional component of the lymph node (Figure 7). There is the largest value of the total coefficient in the tracheobronchial lymph node, and a smaller value in the mesenteric lymph node (Figure 7). The mesenteric lymph node is more susceptible to senile changes. It is parametrically different from the base level on the part of structure, hydration and trace elements. The total coefficient is determined by the low magnitude for the mesenteric lymph node.

DISCUSSION

The need to study regional lymph nodes follows from the emergence of lymphatic (lymphoid) theory of aging [1,5,7] and the concept of lymphatic region [4]. This is confirmed in the paradigm: the morphofunctional status of the lymph node determines the state of the tissue microdistrict [5-8]. Morphophysiology features of respiratory system and gastrointestinal tract necessarily affect the morphology of lymphatic region regional lymph nodes. We cannot consider isolated age changes without a complex relationship between the lymphatic region and regional lymph nodes. We understand that lymph nodes perform control at the exit from the lymphatic region [1,4].

The results showed that age-dependent changes occur differently in the mesenteric and tracheobronchial lymph nodes. The aging dynamics of regional lymph nodes may be closely related to the drainage features of the lymphatic region of the organ. The lymphatic region of the respiratory system and gastrointestinal tract have different antigenic loads when in contact with the external environment during different periods of life. Different antigenic load causes accelerated aging of the mesenteric lymph node compared to the tracheobronchial lymph node.

The mesenteric lymph node is more susceptible to senile changes. Parameters differ significantly from the base level for structure, hydration, and trace elements. We assume that the difference in structural response to aging depends on the initial morphotype of the lymph node and belonging of a certain lymphatic region [2,4].

There is a real relationship between trace elements and the structural and functional organization of lymph nodes in aging. Trace elements have a direct or indirect association with enzymes involved in lymphoid cell proliferation. Lack of trace elements and enzymes results in low proliferation of immunocompetent cells and reduced size of lymph node compartments. There is the formation of a certain lymph node morphotype with reduced drainage and immune function in aging.

The mesenteric lymph node is more susceptible to senile changes than the tracheobronchial lymph node. The synergy of the response of functional components of the lymph node gives reason to extrapolate the results to the entire lymphatic region. The lymphatic region includes the «organ – lymph node» system, and the organ is dominant due to direct contact with the external environment [4]. The regional principle of peripheral lymphoid organs aging has received evidence according to the concept of the lymphatic region.

CONCLUSION

The concept of the lymphatic region is recognized as promising for the development of lymphology. This concept contributes to clarifying the morphological restructuring of lymph nodes in aging. Structural-physiological mechanisms of lymph node functioning are provided by a complex of functional systems, including structure, hydration and trace elements. Lymph node localization is determinative in the formation of morphofunctional lymph node status in aging. Age-induced changes in mesenteric and tracheobronchial lymph nodes occur with different intensity. The mesenteric lymph node is subject to changes to a greater extent than the tracheobronchial lymph node. Baseline indicators show a difference between visceral lymph nodes. Lymphoid tissue involution, dehydration and trace elements deficiency predominate in the mesenteric lymph node than in the tracheobronchial lymph node. The parameters deviate sufficiently from the base level and the total growth coefficient is low for the mesenteric lymph node. The total growth coefficient for the tracheobronchial lymph node is higher, the parameters deviate little from the basic level. The results presented are of fundamental importance. The results are related to the implementation of the principle of regional determinant for visceral lymph nodes of different lymphatic regions. The idea of lymphoid tissue aging mechanisms is supplemented.

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