



THE ANATOMY AND FUNCTION OF THE HUMAN LYMPHATIC SYSTEM IN AUTOIMMUNE DISEASES

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ABSTRACT

Background: The lymphatic system is important in the regulation of the immune system, in the clearance of antigens and in the maintenance of the balance in the tissue fluids. The evidence is growing more on the contribution of lymphatic dysfunction to the chronic inflammation in autoimmune diseases; however, the structural and functional changes of lymphatic have not been adequately investigated.

Objective: To evaluate anatomical and functional changes of the lymphatic system in autoimmune diseases and determine their association with disease activity and inflammatory markers.

Methodology: The analytical observational research was carried out at Muhammad College of Medicine, Peshawar between January 2025 and June 2025 and involved 72 patients who were confirmed to have autoimmune disorders. Standard disease activity indices were used to help patients fall into active and low/remission groups of the disease. Imaging methods were used to determine morphology of the lymphatics, and pumping frequency, tracer clearance time, and limb volume were used to determine lymphatic performance. Inflammatory and molecular markers including CRP, ESR, IL-6, and VEGF-C were analyzed. Statistical analysis was performed using SPSS, and $p \leq 0.05$ was considered significant.

Results: Patients with active disease showed significantly enlarged lymph nodes, cortical thickening, dermal backflow, and dilated lymphatic vessels compared to remission patients. Functional assessment revealed reduced lymphatic pumping frequency and prolonged clearance time in active disease ($p < 0.001$). Inflammatory markers including CRP, ESR, and IL-6 were significantly elevated, while VEGF-C levels suggested compensatory lymphangiogenesis. Lymphatic dysfunction was strongly associated with disease activity and clinical edema.

Conclusion: Autoimmune disease activity is associated with significant structural and functional impairment of the lymphatic system. Lymphatic evaluation may serve as a novel biomarker for disease severity and could represent a potential therapeutic target in chronic inflammatory disorders.

Keywords: Lymphatic system, autoimmune disease, inflammation, lymphangiogenesis, VEGF-C, immune regulation

INTRODUCTION

Autoimmune diseases are persistent inflammatory diseases caused by immune dysfunction whereby the immune response is not regulated to act on self-antigens resulting in progressive tissue damage and organ dysfunction. Conventionally, studies concentrated on immune cells, cytokines and genetic predisposition, but now increasing interest is centered on the involvement of the lymphatic system in the preservation of immune homeostasis. The lymphatic system carries interstitial fluid, antigens and immune cells that are present in the peripheral tissues to the lymph nodes where immune response is controlled and tolerance maintained [1-3].

In physiological conditions, effective lymphatic drainage eliminates inflammatory mediators and stops the inflammation in the tissues. In autoimmune diseases, the sustained induction of immunological processes causes prolonged antigen exposure at lymph node level, which causes lymphoid hyperplasia and remodelling of the architecture. Persistent cytokine release may also affect the lymphatic vessels and make them less contractile and less capable of draining. Therefore, inflammatory mediators build up in tissues, continuing the disease activity and causing flare episodes [4-6].

Experimental and clinical experiments indicate that lymphatic vessels are engaged in immune modulation as opposed to being passive conduits. In chronic inflammatory diseases, but these new vessels tend to induce ineffective drainage, altered lymphangiogenesis mediated by vascular endothelial growth factors (VEGF-C/VEGF-D). Such self-contradictory lymphatic dilation and functional insufficiency could be the cause of enduring edema and inflammation, which is observed in autoimmune diseases [7-9].

Despite its potential importance, lymphatic involvement in autoimmune diseases remains under-investigated in clinical practice. Most disease activity assessments rely on laboratory markers and clinical symptoms, which may not fully reflect underlying inflammatory burden. Evaluating structural and functional lymphatic changes could therefore provide additional insights into disease mechanisms and help identify novel therapeutic targets [10-12].

The present study was designed to assess anatomical and functional alterations of the lymphatic system in patients with autoimmune diseases and to determine their relationship with inflammatory activity and disease severity.

METHODOLOGY

This analytical observational study was conducted at Muhammad College of Medicine, Peshawar over a period of six months from January 2025 to June 2025. The research was conducted to evaluate structural and functional changes in the human lymphatic system in patients with autoimmune diseases and to establish their relationship with activity of inflammatory diseases

Consecutive non-probability sampling was the method used to enroll 72 patients. The sample population was comprised of adult patients (18-65 years old) with a confirmed diagnosis of autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, psoriasis/psoriatic disease and multiple sclerosis) according to accepted clinical and laboratory criteria. Malignant patients, acute infections, primary lymphedema, history of lymphatic surgery, uncontrolled diabetes mellitus, severe cardiovascular disease, or pregnancy were eliminated to prevent confounding on lymphedema physiology.

Informed consent was obtained and demographic and clinical data were captured after informed consent, such as age, gender, duration of disease, history of taking medication and status of disease

activity. Based on conventional disease-specific activity scoring scales (e.g. DAS-28, SLEDAI, EDSS as required), disease activity was classified into active and low/remission.

All participants were assessed under the imaging and functional assessment to evaluate the lymphatic system. The high-resolution ultrasonography and magnetic resonance lymphatic imaging were used to determine lymph node morphology and lymphatic vessel characteristics when necessary. Measurements of parameters were made on lymph node size, cortical thickness, hilum status, vessel dilation, and dermal backflow. The performance of the functional lymphatics was tested through measuring the lymphatic pumping frequency, time of clearance of tracers and the volume difference of the limbs.

Blood samples were collected under aseptic conditions for laboratory investigations. Inflammatory and immunological markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), and vascular endothelial growth factor-C (VEGF-C) were measured using standard automated laboratory techniques and ELISA methods where required.

All collected data were entered and analyzed using SPSS version 26 (IBM Corp., USA). Continuous variables were expressed as mean $\pm$ standard deviation while categorical variables were presented as frequencies and percentages. Independent t-test was applied for comparison of continuous variables between groups and Chi-square test for categorical variables. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The patients aged 72 in the study were mostly females with auto immunity diseases. Active disease group patients were observed to have much longer disease period and more frequent steroid use than remission group patients. Active disease activity was also strongly related to clinical edema.

Table 1: Demographic & Clinical Characteristics

Variable	Total (n=72)	Active disease (n=40)	Low/Remission (n=32)	p-value
Age (years), mean $\pm$ SD	36.8 $\pm$ 11.4	37.6 $\pm$ 11.1	35.9 $\pm$ 11.9	0.52
Female, n (%)	52 (72.2)	30 (75.0)	22 (68.8)	0.56
Disease duration (years), mean $\pm$ SD	5.2 $\pm$ 3.4	6.1 $\pm$ 3.6	4.1 $\pm$ 2.9	0.01
Steroid use, n (%)	38 (52.8)	28 (70.0)	10 (31.3)	<0.001
DMARDs, n (%)	49 (68.1)	30 (75.0)	19 (59.4)	0.16
Biologics, n (%)	17 (23.6)	12 (30.0)	5 (15.6)	0.15
Clinical limb edema, n (%)	21 (29.2)	17 (42.5)	4 (12.5)	0.006

The most common autoimmune disorder was rheumatoid arthritis and secondly systemic lupus erythematosus. The study population was a representative of a wide range of immune-mediated disorders. This distribution permitted a comparison of lymphatic malfunction in various autoimmune pathologies.

Table 2: Distribution of Autoimmune Diseases

Autoimmune disease category	n (%)
Rheumatoid arthritis	20 (27.8)
Systemic lupus erythematosus	16 (22.2)

Sjögren syndrome	12 (16.7)
Psoriasis/Psoriatic disease	14 (19.4)
Multiple sclerosis	10 (13.9)

Imaging demonstrated significantly enlarged lymph nodes and cortical thickening in active disease patients. The presence of dermal backflow and lymphatic dilation of the vessels were significantly higher in the active group, which is an indication of poor lymphatic drainage. Large lymphatic malformations were highly associated with the presence of inflammatory disease.

Table 3: Anatomical / Imaging Lymphatic Findings

Imaging variable	Total	Active	Remission	p-value
Enlarged lymph nodes	33 (45.8)	25 (62.5)	8 (25.0)	0.002
Largest lymph node size (mm)	12.6 ± 4.1	14.1 ± 4.0	10.7 ± 3.4	<0.001
Cortical thickening	29 (40.3)	22 (55.0)	7 (21.9)	0.005
Loss of fatty hilum	18 (25.0)	15 (37.5)	3 (9.4)	0.007
Dilated lymphatic vessels	27 (37.5)	20 (50.0)	7 (21.9)	0.01
Dermal backflow	19 (26.4)	16 (40.0)	3 (9.4)	0.003
Fibrotic channels	22 (30.6)	17 (42.5)	5 (15.6)	0.01

It was found that active patients with the disease had a much slower lymphatic pumping and slower tracer clearance. There was a significant increase in inflammatory biomarkers such as CRP, ESR and IL-6 in patients with compromised lymphatic. VEGF-C had also considerably increased and this indicated compensatory lymphangiogenesis.

Table 4: Functional Lymphatic Indices & Inflammatory Markers

Variable	Total	Active	Remission	p-value
Pumping frequency	4.3 ± 1.6	3.7 ± 1.4	5.1 ± 1.4	<0.001
Clearance time (min)	46.9 ± 18.7	55.6 ± 17.9	36.1 ± 14.2	<0.001
Limb volume difference (%)	6.8 ± 5.7	9.1 ± 6.1	3.9 ± 3.6	<0.001
CRP (mg/L)	12 (6–26)	19 (10–33)	6 (3–11)	<0.001
ESR (mm/hr)	32.4 ± 17.2	41.1 ± 16.4	21.6 ± 12.6	<0.001
IL-6 (pg/mL)	14.8 ± 7.9	18.1 ± 7.5	10.6 ± 6.2	<0.001
VEGF-C (pg/mL)	386 ± 128	442 ± 121	316 ± 108	<0.001

Active autoimmune disease was strongly linked with lymphatic dysfunction. The risk of lymphatic impairment was the greatest among patients with high CRP and clinical edema. Dermal backflow was the most strongly correlated with the severity of the disease.

Table 5: Association of Lymphatic Dysfunction With Disease Activity

Predictor	Dysfunction Present (n=34)	Absent (n=38)	p-value
Active disease	26 (76.5)	14 (36.8)	<0.001
Clinical edema	18 (52.9)	3 (7.9)	<0.001
CRP >10 mg/L	23 (67.6)	9 (23.7)	<0.001
Dermal backflow	17 (50.0)	2 (5.3)	<0.001

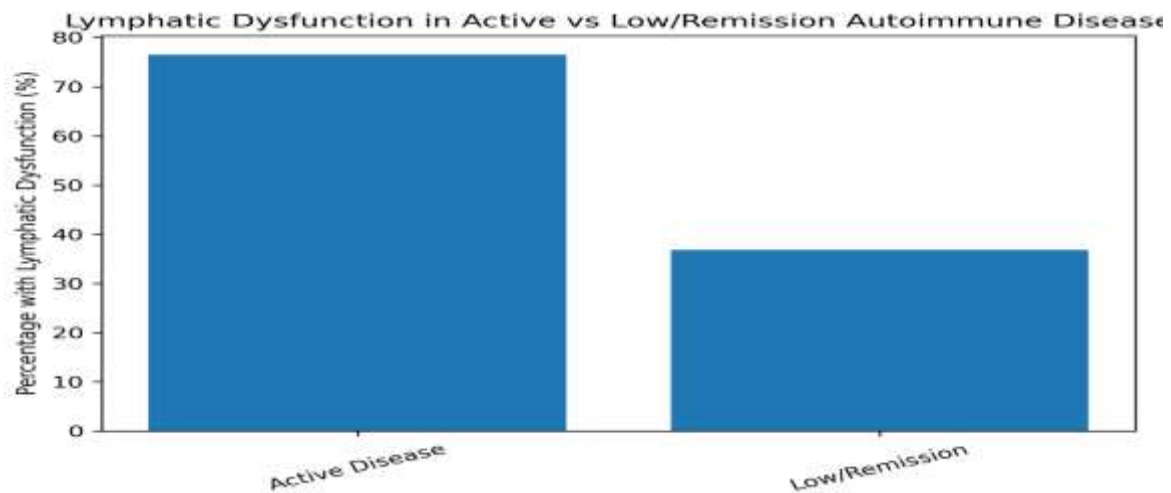


Figure 1

Comparison of lymphatic dysfunction between active and low/remission autoimmune disease groups. Patients with active disease demonstrated markedly higher prevalence of lymphatic impairment, highlighting the relationship between inflammatory activity and lymphatic drainage failure.

DISCUSSION

The current research assessed structural and functional changes of the lymphatic system in autoimmune diseases and showed a strong correlation between lymphatic dysfunction and the disease activity. Active patients had a greater lymph node, cortical thickening, dermal backflow, and lymphatic pumping capacity in comparison with the remission. These results indicate the idea that the lymphatic circulation is not only a passive drain system but also an active factor that controls the immune homeostasis [13-15].

Autoimmune disorders cause chronic inflammation, which results in persistent antigen presentation and the transport of immune cells in lymph nodes. Cortical thickening and lymphoid hyperplasia is a result of persistent immune stimulation, which justifies the outcome of the size increase in lymph nodes and cortical thickening seen in this study. The common fatty hilum loss and irregular lymphatic channels are also evidence of the structural remodeling due to the long-term exposure to the effect of cytokines of the inflammation [16-18].

Another important functional in the present study was the delayed clearance of tracer and decreased lymphatic contractility in active disease. Lymphatic pumping is impaired, and this decreases the ability to remove the effect of inflammatory mediators of tissues, which leads to the accumulation of cytokines and immune complexes locally. This leads to an inflammatory cycle which perpetuates itself hence the higher CRP, ESR and IL-6 levels in the patients with active disease. Thus, lymphatic dysfunction seems to be the contributor of the disease persistence instead of a secondary effect [19, 20]. The presence of high VEGF-C in active disease warrants the idea of compensatory lymphangiogenesis. During chronic inflammation, the body tries to re-establish fluid homeostasis and immune trafficking through the development of new lymphatic vessels. Nevertheless, these new vessels are frequently still developing and functionally inefficient, the reason why lymphatic dilation was always associated with poor clearance in our patients. This observation shows that lymphangiogenesis in autoimmune disease is structurally intact but functionally impaired [21].

The clinical significance of lymphatic dysfunction is emphasized because of the significant correlation between dermal backflow, edema, and inflammatory activity. Lymphatic dysfunction patients had higher chances of having high CRP and active disease status. This indicates that lymphatic imaging can be used as objective biomarker to monitor the disease and can be used in predicting the risk of a flare. Determining lymphatic functioning could thus be used to supplement traditional lab indicators in measuring the severity of autoimmune disease [22].

Overall, the findings support emerging immunological concepts that lymphatic vessels actively regulate immune tolerance, antigen transport, and inflammatory resolution. Dysfunction of this system may contribute to chronicity of autoimmune diseases and explain why some patients remain symptomatic despite adequate immunosuppressive therapy.

CONCLUSION

Lymphatic structural abnormalities and impaired drainage are significantly associated with increased autoimmune disease activity and systemic inflammation. Active disease shows reduced lymphatic contractility, delayed clearance, and compensatory but ineffective lymphangiogenesis. Evaluation of lymphatic function may serve as a novel imaging biomarker and therapeutic target in autoimmune disorders, providing new opportunities for disease monitoring and future treatment strategies.

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