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EVALUATION OF HAEMATOLOGICAL PARAMETERS CHANGES AND D-DIMER VALUES AMONG SUDANESE SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IN KHARTOUM STATE

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem inclusion and is related with significant morbidity and mortality. Hematologic manifestation abnormalities are common in systemic lupus erythematosus (SLE), both at the time of diagnosis and all through the illness. The major hematologic appearances of SLE incorporate anemia, leukopenia, thrombocytopenia, and increased ability for thrombosis. This study was conducted to evaluate the hematological parameters (CBC) changes of SLE and to investigate the clinical significance of D-dimer values in systemic lupus erythematosus (SLE) patients in predicting thrombosis among Sudanese patients in Khartoum state. **Methodology:** Cross sectional case-control study done during the period of May 2020 to August 2021 in Alrayan Specilaized Center and Omdurman military hospital in Khartoum state to evaluate the haematological and coagulation changes among Sudanese patients with systemic lupus erythromatosus. Sixty (60)SLE Patients and 40 apparently healthy individual as control), their age ranged from (15-55) years. **Results:** In systemic lupus erythematosus (SLE) there are significant differences in the mean of RBCs, WBCs, neutrophil, Lymphocyte, platelets count, and D-dimer between the SLE patients group and normal control group (P-value 0.003, <0.001, 0.009, <0.001, <0.001, and 0.001) respectively. This might reflects the effect of SLE on many haematological and coagulation parameters. Out of 60 patients affected by systemic lupus erythromatosus anemia was detected in 24 patients (40%) , leukopenia in 23 patients (38.3%) , lymphopenia in 12 patient (20%), neutropenia in 28 patients (47%), and thrombocytopenia in 13 patients (21.7%). Systemic lupus erythematosus patients had significantly higher D-dimer levels (6.32±5.12), when compared with the control group (0.25±0.04) (P = 0.001). In systemic lupus erythematosus patients, 28 patients (46.7%) out of 60 showed negative D-dimer results (< 0.5 µg/ml) with no thrombosis seen, 11 patients (18.3%) out of 60 showed higher levels of D-dimer (0.5 – 3.0 µg/ml) with thrombosis seen in 4%, 21 patients (35%) out of 60 showed higher levels of D-dimer (> 3.0 µg/ml) with thrombosis seen in 25%. **Conclusions:** The major haematological abnormalities in patients with systemic lupus erythromatosus (SLE) include anemia, leukopenia, and thrombocytopenia, or pancytopenia. This study concluded that the red blood cells (RBCs), white blood cells (WBCs), neutrophils, lymphocytes and platelets were lower in systemic lupus erythromatosus (SLE) when compared with the normal control. D-dimer level in patients with systemic lupus erythematosus (SLE) could be an effective sign in indication of the disease. The level of D-dimer elevates in patients with active disease. D-dimer levels had increased in all patients with thrombosis.

KEYWORDS: Systemic lupus erythematosus**,** Hematological parameters changes, D-dimer values.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple lesions that cause inflammation and the production of autoantibodies.[1] Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem involvement and is associated with significant morbidity and mortality. Genetic, immunological, endocrine, and environmental

factors influence the loss of immunological tolerance against self-antigens leading to the formation of pathogenic autoantibodies that cause tissue damage through multiple mechanisms.[1]

Anemia is present in more than 50% of patients with SLE and most commonly is anemia of chronic disease. Other causes of anemia in SLE may include iron deficiency anemia, coomb's positive autoimmune hemolytic anemia, red blood cell aplasia and microangiopathic hemolytic anemia which may be associated with antiphospholipid antibody syndrome. Leukopenia secondary to neutropenia or lymphopenia is also very frequent and can be severe. Thrombocytopenia can be mild or severe and may be associated with antiphospholipid antibody syndrome and autoantibodies against platelets, glycoprotein IIb/IIIa or thrombopoietin receptor. Pancytopenia is not infrequent and may occasionally be associated with myelofibrosis. Soft non-tender lymphadenopathy is common in SLE, although rare cases of histiocytic necrotizing lymphadenitis have been reported (Kikuchi-Fujimoto disease). Splenomegaly is common in SLE, while splenic atrophy and asplenism have been reported.[1]

More than 90% of cases of SLE occur in women, frequently starting at childbearing age systemic autoimmune disease (or autoimmune connective tissue disease) in which the body immune system mistakenly attacks healthy tissue. When the immune system is functioning normally, it makes proteins called antibodies that protect against pathogens such as viruses and bacteria. Lupus is characterized by the presence of antibodies against a person's own proteins; these are most commonly anti-nuclear antibodies, which are found in nearly all cases. These antibodies leadto inflammation. Although the underlying cause of autoimmune diseases is unknown, most believe that lupus results from both genetic and environmental stimuli. There are many kinds of lupus. The most common type is systemic lupus erythematosus (SLE), which affects many internal organs in the body. SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. The course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. The disease occurs nine times more often in women than in men, especially in women in child-bearing years ages 15 to 35. In adults, raynaud pleuritis and sicca are twice as common as in children and adolescents. The classic presentation of a triad fever, joint pain, and rash in a women of childbearing age should prompt investigation into the diagnosis of SLE. Hematologic manifestations occur (eg, cytopenias, such as leucopenia, lymphopenia, anemia, or thrombocytopenia). In patients with suggestive clinical findings, a family history of autoimmune disease should raise further suspicion of SLE.[2]

Poor access to care, late diagnosis, less effective treatments, and poor adherence to therapeutic regimens may increase the damaging effects of SLE, causing more complications and an increased risk of death.[3]

SLE can limit a person's physical, mental, and social functioning. These limitations experienced by people with SLE can impact their quality of life, especially if they experience fatigue. Fatigue is the most common symptom negatively affecting the quality of life of people with SLE.[4,5]

Annual incidence estimates were much higher for women than men in Michigan (9.3 vs 1.5 per 100,000 people). Hispanic women had higher incidence estimates than men in San Francisco County (7.2 vs 0.6 per 100,000 people) and Manhattan (6.5 vs 1.3 per 100,000 people), as well as Asian women in San Francisco County (8.9 vs 0.3 per 100,000 people) and Manhattan (6.6 vs 0.5s per 100,000 people).[6,7]

Previous studies have reported the dysregulation of coagulation and complement-related genes and proteins in patients with SLE, suggesting that coagulation cascade and complement system have a role in pathogenic process of SLE.[8]

As fundamental biological processes, the individual constituents of coagulation cascade and complement system are finely orchestrated to form two distinct multi-component networks.[9]

The interplays between complement system, coagulation cascade and inflammatory response have been reported to be associated with disease severity in various clinical and experimental settings. However, the potential role of these interactions for disease severity in the patients with SLE has yet to be determined.[10,11]

MATERIALS AND METHODS

Cross sectional case-control study done during the period of May 2020 to August 2021 in Alrayan Specilaized Center and Omdurman military hospital in Khartoum state to evaluate the haematological and coagulation changes among Sudanese patients with systemic lupus erythromatosus. Sixty (60) SLE Patients and 40 apparently healthy individual as control), their age ranged from (15-55) years.

Inclusion criteria includes Sudanese adult patients of both sexes, while exclusion criteria includes patients who are treated with anticoagulant.

Haematological parameters (CBC) estimation were done using EDTA anticoagulated blood by Sysmex KX21N. Coagulation parameters (D-dimer) were done using tri-sodium citrate (3.2%) anticoagulated blood by (**Coatron® M2**) coagulation analyzer. Analysis of the blood serum done within three hours from the time of collection using (**Coatron® M2**) for coagulation

tests.Volunteers filled the questionnaire forms and checked for exclusion and inclusion situations of them before phlebotomy process begins.

Preparation of platelet poor plasma (PPP): The blood samples were collected from patients and controls in tri-sodium citrate (3.2%) anticoagulant (ratio1:9). Platelet poor plasma sample were prepared by centrifugation at 2000g for 15 min. The plasma samples were stored at 20 ± 5^{O}C and tested within three hours for D-dimer measurement.

Data analysis: All data are presented as mean ± SD using Statistical Package for the Social Sciences (SPSS), unless otherwise noted. Statistical comparisons were performed using unpaired student's t-test with $p<0.05$ considered as significant.

RESULTS

A total of 60 Systemic lupus erythematosus (SLE) patients with the mean age was 28 years, a cases were included according to inclusion criteria. Table (1) shows the Comparison of RBCs, WBCs, Neutrophil, Lymphocyte and Platelets among SLE patients and normal control. The mean of RBCs, WBCs, Neutrophil, Lymphocyte and Platelets count is lower than mean of normal control, which reflects the effect of SLE on these haematological and coagulation parameters.

Table (4.1): Descriptive of mean (SD) of RBCs, WBCs, Neutrophil, Lymphocyte and Platelets count among SLE patientsand normal control.

Group	SLEmean (SD) (n=60)	Normal control mean (SD) (n=40)
RBCS	4.19 (0.45)	4.48 (0.48)
WBCs	5.98 (2.70)	7.37 (2.41)
Neutrophil	3.80 (2.31)	4.48 (2.05)
Lymphocytes	1.78 (0.80)	2.62 (0.88)
Platelets	157.2 (43.7)	244.1 (76.2)

Table (4.2) shows the Comparison of mean differences of RBCs, WBCs, Neutrophil, Lymphocyte, Platelets count, and D-dimer among patients group and control group. There are significant differences in the mean of RBCs, WBCs, neutrophil, Lymphocyte, platelets count, and D-dimer between the SLE patients group and normal control group (0.003, <0.001, 0.009, <0.001, <0.001, and 0.001) respectively. This might reflects the effect of SLE on many haematological and coagulation parameters.

Out of 60 patients affected by systemic lupus erythromatosus anemia was detected in 24 patients (40%), leukopenia in 23 patients (38.3%), lymphopenia in 12 patient (20%), neutropenia in 28 patients (47%), and thrombocytopenia in 13 patients (21.7%).

Table (4.2): Comparison of the mean differences of RBCs, WBCs, neutrophil, lymphocyte, platelets count, and D-dimer among SLE patients group and normal control group.

Group	p-value
RBCS	0.003
WBCs	< 0.001
Neutrophil	0.009
Lymphocytes	< 0.001
Platelets	< 0.001
D-dimer	0.001

Systemic lupus erythematosus patients had significantly higher D-dimer levels (6.32±5.12), when compared with the control group (0.25±0.04) (P = 0.001).

In systemic lupus erythematosus patients, 28 patients (46.7%) out of 60 showed negative D-dimer results (< 0.5 µg/ml) with no thrombosis seen, 11 patients (18.3%) out of 60 showed higher levels of D-dimer (0.5 – 3.0 µg/ml) with thrombosis seen in 4%, 21 patients (35%) out of 60 showed higher levels of D-dimer (> 3.0 µg/ml) with thrombosis seen in 25%.

The most widely recognized reasons for raised D-dimer without any self evident of thrombosis were SLE flare and infection. D-dimer levels were generally raised for some months before thrombosis.

All SLE cases with thrombosis had elevated D-dimer, but SLE cases without thrombosis had normal or elevated D-dimer levels.

In systemic lupus erythematosus patients, 13 patients (21.3%) patients developed thrombocytopenia (platelet count less than 100×10^3/cumm), and 52.7% of the patients showed decreased platelet count (between 100 - 150×10^3/cumm). Patients with systemic lupus erythematosus showed significantly lower platelet count than the control group ($157.2\pm43.7\times10^3$/cumm) vs ($244.1\pm76.2\times10^3$/cumm) respectively ($p<0.001$).

DISCUSSION

This study was cross sectional case-control study conducted to evaluate the haematological and coagulation changes among Sudanese patients with systemic lupus erythromatosus in 60 consecutive patients with recurrently active SLE. Each was tested for hematological parameters and D-dimers.

In the present study out of 60 patients affected by systemic lupus erythromatosus anemia was detected in 24 patients (40%), leukopenia in 23 patients (38.3%), lymphopenia in 12 patient (20%), neutropenia in 28 patients (47%), and thrombocytopenia in 13 patients (21.7%) and these findings Were agree with Chinese study done by Chen J, et al, which reported that SLE patients had hematological abnormalities, (52.1%) had anemia, (30.9%) had a white lood cells (WBCs) count < 4.0 x 10(9)/L and 57 patients (24.2%) had a platelet count < 100 x 10(9)/L[12] and also agree with study reported by Vaya A, et al, in which they suggested that 26 patients out of 105 SLE patients were anemic.[13]

Acroatian study done by Ahmed A, et al, shows similar results to our results and concluded that Peripheral cytopenias occur commonly in SLE and affecting 80% of patients.[14]

Regarding the Leucopenia and Erythropenia, the mean (SD) ofWBCs for this study was 5.98 (2.70) and RBCs was 4.19 (0.45) were lower when compared with normal control and show statist ically significant P.value (< 0.001, 0.003) respectively.

Other study in USA done by Beyan E, etal 2009 among hematological presentation in systemic lupus erythematosus, (WBCs was (43%) and RBCs was (52%) with findings which agree with our study.[15]

In the present study the results show thrombocytopenia in 13 patients (21.7%) and this finding was agree with Bashal F, finding which reported that the prevalence of thrombocytopenia ranging from 7 to 30% in large series of patients with SLE.[16] From theabove results there was obvious effect of SLE on haematological parameter.

We found that abnormally elevated D-dimer levels, particularly peak values >3.0 µg/ml, identified a group at high risk for thrombosis. During study follow-up, 25% developed thrombosis. By contrast, in the group with D-dimer <0.5 µg/ml, none developed thrombosis. Of those with D-dimer between 0.5 and 3.0 µg/ml during study follow-up, 4% developed thrombosis.

For the purposes of this study, we arbitrarily defined the date of the thrombotic event as the date when the diagnosis of thrombosis was made; however, in many of these patients, the clotting event likely was under way for several months or more before the diagnosis was made. Conversely, for thrombotic events that have a decisive onset (microangiopathic antiphospholipid syndrome, catastrophic antiphospholipid syndrome, pulmonary embolus, or deep vein thrombosis DVT), it should be possible to estimate accurately the interval between the onset of the hypercoagulable state and the onset of the thrombotic event.[17]

The level of D-dimer was positively correlated with SLE disease activity index (SLEDAI) score (r = 0.598, P = 0.000), and was associated with anti-dsDNA antibody, ESR, C-reactive protein (CRP) and complement C(3) and C(4).[18]

Further, recent studies suggest that the interaction is not confined to the coagulation cascade and complement system. Specifically, the coagulation cascade and complement system can interact with each other indirectly through the regulation of inflammatory mediators.[19,20,21] For example, an interaction between C5a and inflammatory cytokines have been demonstrated, including an effect on the production of tumor necrosis factor (TNF)-α and interleukin (IL)-6.[22] Then, these cytokines can enhance the activation of coagulation cascade by promoting the expression of coagulants and inhibiting the production of anticoagulants.[23] The interplays between complement system, coagulation cascade and inflammatory response have been reported to be associated with disease severity in various clinical and experimental settings.[19,20] However, the potential role of these interactions for disease severity in the patients with SLE has yet to be determined.

CONCLUSION

The major haematological abnormalities in patients with systemic lupus erythromatosus (SLE) include anemia, leukopenia, and thrombocytopenia, or pancytopenia.

This study concluded that the red blood cells (RBCs), white blood cells (WBCs), neutrophils, lymphocytes and platelets were lower in systemic lupus erythromatosus (SLE) when compared with the normal control.

Anemia and neutropenia are common in systemic lupus erythematosus (SLE) but patients with severe neutropenia makes patients susceptible to infection.

Cytopenias are major hematological manifestations of SLE and maybe it is evidence of active or severe diseases that may lead to increased mortality risk.

D-dimer level in patients with systemic lupus erythematosus (SLE) could be an effective sign in indication of the disease. The level of D-dimer elevates in patients with active disease. D-dimer levels had increased in all patients with thrombosis.

Systemic lupus erythematosus (SLE) patients with normal D-dimer levels decrease the risk for thrombosis. Systemic lupus erythematosus (SLE) patients with elevated D-dimer levels more than 3.0 µg/ml make patients more predispose for thrombosis.

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