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Serum Ferritin, P53 and IgE interplay in patients with Systemic Lupus Erythematosus (SLE)

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Abstract

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that is fast becoming a common condition among blacks, including Nigerians. Its prevalence, frequency, and severity may be influenced by immune status, race, genetic, and environmental factors. This study investigated the interaction of serum ferritin, IgE, p53 and a few inflammatory markers (CRP and RA) in SLE in our study population.

Materials and Methods: A total of eighty consented male and female subjects consisting of 30 ANA and Anti-ds-DNA positive as classical SLE cases, 42 ANA and Anti-ds-DNA negative controls, and 8 ANA positive and anti-ds-DNA negative were recruited into the study. Serum samples were analyzed for Ferritin and Total IgE by a chemiluminescence method and *p53*, RF, and CRP by ELISA techniques. Statistical analysis was carried out using the IBM SPSS incorporated, version 20, (Illinois, Chicago).

Results: Ferritin and p53 levels were significantly increased ($t = 0.001$, $p < 0.05$ and $t = 0.008$, $p < 0.05$ respectively), in the SLE positive cases compared to the Negative control and ANA positive control participants. The levels of total IgE, RF and CRP were not significantly different in the three groups, ($t = 0.247$, 0.153 and 0.440 respectively, $p > 0.05$). However, serum IgE levels were increased in the male participants compared to the female and correlated with age. The levels of CRP correlated with p53 and age while ferritin was observed to correlate with p53, CRP, and RF levels.

Conclusion: This study showed gender prevalence and preponderance to the female population, ratio of females to males, 4:1, with a mean age of 33.83 years (male) and 34.71 years (female). The elevated levels of ferritin and p53 along with the correlation among SLE participants suggests an important intersection between inflammation and apoptosis, with a promising application as biomarkers, possibly for the monitoring of the prognosis and management of this disease.

Keywords: C-reactive protein (CRP), Ferritin, Rheumatoid Factor (RF), Systemic Lupus Erythematosus (SLE), Total IgE, *p53*.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that is fast becoming a common condition among blacks, including Nigerians (1-2). It is up to nine times more common in women than men (3) The pathogenesis is unclear but appears to result from environmental factors interacting with a genetically susceptible host (4). However, geography and race may affect the prevalence, frequency, and severity of clinical and laboratory manifestations

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of SLE. Many rheumatic diseases are characterized by the presence of one or more antinuclear antibodies (ANA) in the absence of anti-dsDNA. Anti-dsDNA autoantibodies are highly specific for lupus and have been found to fluctuate with disease activity. They are rarely associated with other autoimmune diseases or infections. It is, therefore, one of the diagnostic criteria for SLE.

Ferritin, an iron storage protein, is an acute phase reactant which is elevated in inflammation, autoimmune disorders, chronic infections, and liver disease. Varnasa et al. (5) have reported elevated serum levels of ferritin in SLE patients relative to those of control participants as a promising biomarker in SLE. P53 is a tumor suppressor gene that protects the body from DNA damage and cancer. P53 controls cell cycle activity, leading to apoptosis of auto-reactive cells, preventing these cells' proliferation and differentiation (6, 7). As a result, any mutations in the p53 gene may cause cancer and autoimmune diseases (8). One manifestation of SLE is abnormalities in apoptosis, programmed cell death in which aging or damaged cells are neatly disposed of as a part of normal growth or functioning. IgE has also been considered a biomarker for immune dysregulation, as observed in patients with partial T cell immunodeficiencies (9). Few studies have evaluated the IgE levels in SLE patients (10). Elevated serum IgE levels have been reported in SLE, but associations with disease risk and characteristics remain unresolved (11). Other inflammatory markers such as Rheumatoid factor (RF), proteins produced by the immune system that can attack healthy tissue in the body, and C-reactive protein (CRP), whose levels have been reported to rise in response to inflammation, may also be implicated in SLE. This study was therefore designed to determine the serum levels of ferritin, p53, IgE, RF, and CRP in patients with SLE compared with controls to determine their possible roles in systemic lupus erythematosus (SLE) and establish relationships between these biomarkers in systemic lupus erythematosus (SLE) patients in our study population.

MATERIALS AND METHODS

Study Population

This is a cross-sectional prospective study design consisting of eighty (80) participants (16 male and 64 female) with SLE and controls with an age range between 18 and 60 years recruited from Lagos State University Teaching Hospital, Ikeja, a tertiary health institution that receives referrals from different parts of the state and beyond. Participants were categorized into three (3) groups based on ANA and anti-dsDNA antibody status:

Group I: 30 ANA and anti-dsDNA positive patients as the classical SLE-positive cases

Group II: 42 ANA and anti-dsDNA negative participants as the negative control group, and

Group III. 8 ANA positive and anti-dsDNA negative participants as the ANA positive cases

Exclusion Criteria

Patients with other known autoimmune diseases, such as rheumatoid arthritis, haematopoietic disorders, parasitic infections, asthma, and other allergies that may influence total IgE and ferritin levels, were excluded from the study.

Inclusion Criteria

All subjects, male and female, aged between 18 and 60, who fulfilled the selective criteria as discussed above (cases and controls) in groups I, II, and III were included in the study.

Ethical Approval

The study received ethical approval from the Lagos State University Teaching Hospital Ethical Committee Board (LHREC 10/ 06/ 407). The

participants provided written informed consent, and a well-structured questionnaire reflecting their demographic information was also administered. Responses were kept confidential.

Experimental Design and Analysis

Ten (10mls) of venous blood samples were collected by venipuncture from the volunteered participants and put into plain tubes. The blood samples were left to clot, and the serum separated and stored at -20oC until analysis. Serum ferritin and total IgE levels in the participants were quantified by an automated chemiluminescence method described by Baeyens et al. (12). The ANA and DS-DNA, p53 protein, CRP, RF were measured by an ELISA method as described by Engvall and Perlman., (13).

Statistical Analysis

This was done using the IBM SPSS incorporated version 20 software (Illinois, Chicago, USA). Descriptive statistics were expressed as means ± SEM. ANOVA was used to compare the mean within and between the three groups. Student's t-test (2-tailed) was used to compare two groups. Pearson's correlation was used where indicated, and regression analysis was also performed to obtain (adjusted) R2 correlation for age with the variables. A p-value < 0.05 was considered statistically significant.

RESULTS

The mean age for the positive (SLE) case participants was 34.43 years (male, 33.83, and female, 34.71), with an age range of 18 to 56 for the female and 18 to 55 for the male participants. The results of acute phase protein, ferritin, cell cycle apoptotic protein, p53, total IgE and inflammatory markers, RF, and CRP, investigated in this study are presented in Table 1. Increased levels of serum ferritin (2205.97 ± 621.00) and p53 (7.41 ± 1.16) were observed in the SLE cases compared with the negative controls with mean ± SEM serum ferritin (323.95 ± 75.09), p53 (3.22 ± 0.77) ($p<0.05$). The values of P53 in SLE were also significantly increased compared with ANA-positive cases with mean ± SEM serum ferritin (370.99 ± 141.69 and (5.70 ± 1.57, respectively), $p< 0.05$. Similarly, the IgE values were higher in SLE (5079.57±3629.20) compared with controls (320. 86±66. 68) and ANA (348.36±194.47). There was, however, no significant difference in the serum levels of RF and CRP in the 3 groups ($P>0.05$). Figure 1 shows the deferential increase in serum ferritin in SLE patients and p53 in both SLE and ANA compared to controls.

The cross-tabulation of participants with the investigated parameters shows high serum ferritin and p53 levels in both male and female participants in the SLE case group. Positive RF levels were observed in 26.7% of the female participants. The total IgE levels are within normal limits and sustained in both genders but with high levels in only 30% of participants. However, 46.7% of the participants had high CRP levels. 23.8% of the participants had positive RF levels, of which 21.4% were female. Furthermore, high levels of serum p53 were observed in both the male and female participants in the ANA-positive case group. 50% of the participants had high levels of serum ferritin and RF. The details are presented in Tables 2 to 4. The correlations of ferritin, total IgE, p53, CRP, and RF in the three groups, as presented in Table 5, showed total IgE was correlated with age in the SLE case group. A correlation was also observed with the acute phase protein, ferritin, and the inflammatory markers, RF and CRP, in this group. However, the correlation between ferritin and CRP was sustained in the negative control group but was lost in the ANA-positive cases. CRP and P53 were also found to correlate in the negative control group and the ANA positive case group. Furthermore, the correlation between ferritin and p53 was also observed in the negative control group but was lost in the SLE and the ANA Positive case groups. CRP also correlated with age in the negative control group.

TABLE 1: ANOVA oF Total IgE, Ferritin, RF, CRP, and p53 in the Three Groups

		N	MEAN± SEM	95% CI	F	Sig.
	SLE Positive	30	5079.57±3629.20*#	2342.99 - 12502.12	11.423	0.0025
Total IgE	Negative Control	42	320. 86±66. 68	186.20 – 455.53		
(IU/ml).	ANA Positive	8	348.36±194.47#	111.50 – 808.21		
	SLE Positive	30	2205. 97± 621.00*#	935. 88 – 347.0	7.325	0.001
Ferritin	Negative Control	42	323. 95± 75.09	172.32 – 475.59		
(ng/ml).	ANA Positive	8	370. 99± 141. 69#	35. 94 – 706.03		
	SLE Positive	30	0.2091± 0.07	0.08 - .34	1. 923	0.153
RF.	Negative Control	42	0.1845± 0.06	0.06 - .31		
(IU/ml)	ANA Positive	8	0.5000± 0.25	0.08 – 1.08		
	SLE Positive	30	12.31±2.24	7.73 – 16. 89	0. 831	0.440
CRP	Negative Control	42	8.76± 1. 81	5.11 – 12.41		
(ng/ml).	ANA Positive	8	8.49± 4.71	2. 64 – 19.62		
	SLE Positive	30	7.41± 1.16*#	5.04 - 9.77	5.166	0.008
P53	Negative Control	42	3.22± 0.77	1.67 – 4.77		
(ng/ml).	ANA Positive	8	5.70±1.57*#	1.98 - 9.42		

*Significant difference between cases and controls, # between case (SLE and ANA) at p< 0.0**5**
KEY: RF - Rheumatoid factor CRP - C reactive protein

TABLE 2: Cross Tabulation of Sex against total IgE, Ferritin, RF, CRP and P53 in the SLE positive Cases

MODEL	MALE			FEMALE			TOTAL		
	No	% with-in Sex	% of Total	Num	% within Sex	% of Total	Num	% within Sex	% of Total
Total IgE									
Normal	4	66.7%	13.3%	17	70.8%	56.7%	21	70.0%	70.0%
High	2	33.3%	6.7%	7	29.2%	23.3%	9	30.0%	30.0%
Total	6	100.0%	20.0%	24	100.0%	80.0%	30	100.0%	100.0%
Ferritin									
Normal	2	33.3%	6.7%	7	29.2%	23.3%	9	30.0%	30.0%
High	4	66.7%	13.3%	17	70.8%	56.7%	21	70.0%	70.0%
Total	6	100.0%	20.0%	24	100.0%	80.0%	30	100.0%	100.0%
RF									
Negative	6	100.0%	20.0%	16	66.7%	53.3%	22	73.3%	73.3%
Positive	0	0.0%	0.0%	8	33.3%	26.7%	8	26.7%	26.7%
Total	6	100.0%	20.0%	24	100.0%	80.0%	30	100.0%	100.0%
CRP									
Normal	1	16.7%	3.3%	15	62.5%	50.0%	16	53.3%	53.3%
High	5	83.3%	16.7%	9	37.5%	30.0%	14	46.7%	46.7%
Total	6	100.0%	20.0%	24	100.0%	80.0%	30	100.0%	100.0%

P53									
Normal	3	50.0%	10.0%	7	29.2%	23.3%	10	33.3%	33.3%
High	3	50.0%	10.0%	17	70.8%	56.7%	20	66.7%	66.7%
Total	6	100.0%	20.0%	24	100.0%	80.0%	30	100.0%	100.0%

KEY: RF - Rheumatoid factor CRP - C reactive protein

TABLE 3: Cross Tabulation of Sex against total IgE, Ferritin, RF, CRP and p53 in the negative Controls

MODEL	MALE			FEMALE			TOTAL		
	Num	% within Sex	% of Total	Num	% within Sex	% of Total	Num	% within Sex	% of Total
Total IgE									
Normal	3	37.5%	7.1%	26	76.5%	61.9%	29	69.1%	69.1%
High	5	62.5%	11.9%	8	23.5%	19.1%	13	30. 9%	30. 9%
Total	8	100.0%	19.0%	34	100.0%	81.0%	42	100.0%	100.0%
Ferritin									
Normal	5	62.5%	11.9%	26	76.5%	61.9%	31	73. 8%	73. 8%
High	3	37.5%	7.1%	8	23.5%	19.1%	11	26.2%	26.2%
Total	8	100.0%	19.0%	34	100.0%	81.0%	42	100.0%	100.0%
RF									
Negative	7	87.5%	16.7%	25	73.5%	59.5%	32	76.2%	76.2%
Positive	1	12.5%	2.4%	9	26.5%	21.4%	10	23.8%	23.8%
Total	8	100.0%	19.1%	34	100.0%	80.9%	42	100.0%	100.0%
CRP									
Normal	4	50.0%	9.5%	26	76.5%	61.9%	30	71.4%	71.4%
High	4	50.0%	9.5%	8	23.5%	19.1%	12	28. 6%	28.6%
Total	8	100.0%	19.0%	34	100.0%	81.0%	42	100.0%	100.0%
P53									
Normal	6	75.0%	14.3%	26	76.5%	61.9%	32	76.2%	76.2%
High	2	25.0%	4.8%	8	23.5%	19.1%	10	23.8%	23.8%
Total	8	100.0%	19.0%	34	100.0%	81.0%	42	100.0%	100.0%

KEY: RF - Rheumatoid factor CRP - C reactive protein

TABLE 4: Cross Tabulation of Sex against total IgE, Ferritin, RF, CRP and p53 in the ANA Positive Controls

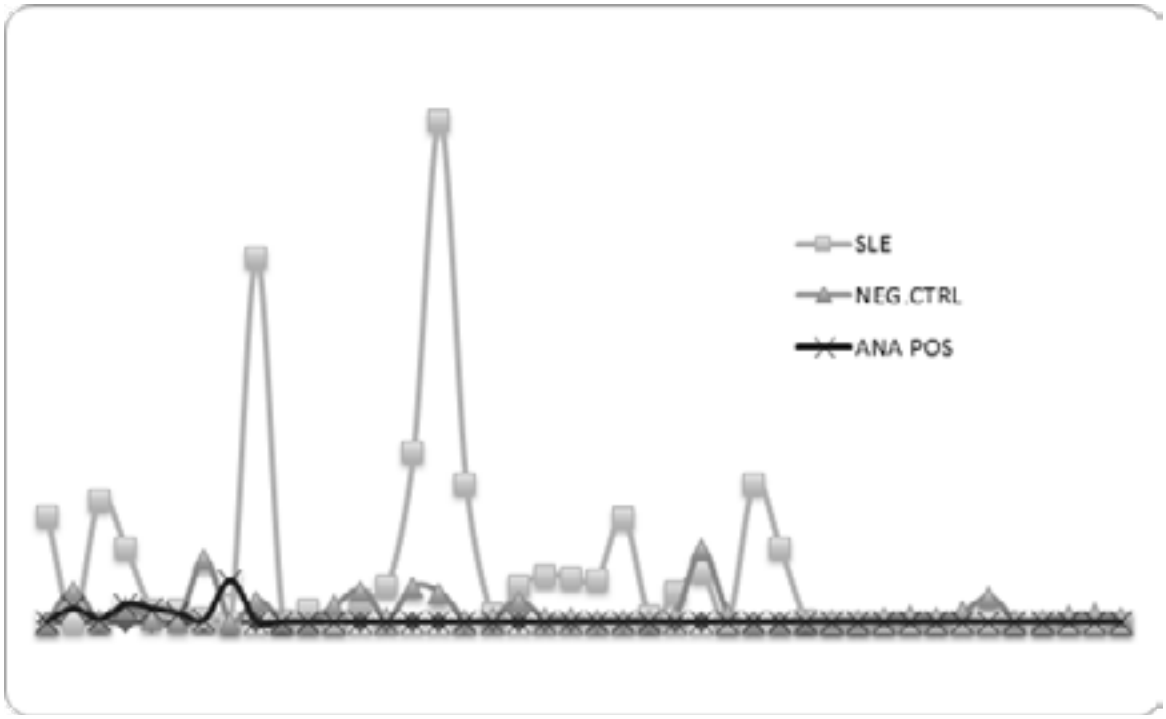
MODEL	MALE			FEMALE			TOTAL		
	Num	% within Sex	% of Total	Num	% within Sex	% of Total	Num	% within Sex	% of Total
Total IgE									
Normal	2	100.0%	25.0%	4	66.7%	50.0%	6	75.0%	75.0%
High	0	0.0%	0.0%	2	33.3%	25.0%	2	25.0%	25.0%
Total	2	100.0%	25.0%	6	100.0%	75.0%	8	100.0%	100.0%
Ferritin									
Normal	0	0.0%	0.0%	4	66.7%	50.0%	4	50.0%	50.0%
High	2	100.0%	25.0%	2	33.3%	25.0%	4	50.0%	50.0%
Total	2	100.0%	25.0%	6	100.0%	75.0%	8	100.0%	100.0%

RF									
Negative	1	50.0%	12.5%	3	50.0%	37.5%	4	50.0%	50.0%
Positive	1	50.0%	12.5%	3	50.0%	37.5%	4	50.0%	50.0%
Total	2	100.0%	25.0%	6	100.0%	75.0%	8	100.0%	100.0%
CRP									
Normal	2	100.0%	25.0%	4	66.7%	50.0%	6	75.0%	75.0%
High	0	0.0%	0.0%	2	33.3%	25.0%	2	25.0%	25.0%
Total	2	100.0%	25.0%	6	100.0%	75.0%	8	100.0%	100.0%
P53									
Normal	1	50.0%	12.5%	2	33.3%	25.0%	3	37.5%	37.5%
High	1	50.0%	12.5%	4	66.7%	50.0%	5	62.5%	62.5%
Total	2	100.0%	25.0%	6	100.0%	75.0%	8	100.0%	100.0%

KEY: RF - Rheumatoid factor CRP - C reactive protein

TABLE 5: Correlations of Total IgE, Ferritin, RF, CRP, and p53 with Age in the 3 Groups

		AGE	**TOTAL IgE**	**FERRITIN**	**RF**	**CRP**	**P53**
SLE Positive Cases N = 30	AGE	1	.402* .028	-.177 .350	-.317 .087	-.025 .896	-.047 .805
	IgE	.402* .028	1	.046 .809	-.099 .603	.203 .281	-.246 .190
	Ferritin	-.177 .350	046 .809	1	.569** .001	. 4 6 5 * * .010	-.004 .985 .022
	RF	-.317 .087	-.099 .603	. 569** .001	1 -.015 . 939	-.015 . 939 1	.909 -.053 .779
	CRP	.025 .896	.203 .281	.465** .010	.022 .909	-.053 .779	1
	P53	-.047 .805	-.246 .190	-.004 .985			
Negative Control N = 42	AGE	1	-.076 .634	.241 .124	-.245 .118	.355* .021	-.006 .969
	IgE	-.076 .634	1	-.052 .744	.101 .523	.196 .213	-.112 .482
	Ferritin	.241 .124	-.052 .744	1	.084 .596	.602** .000	.512** .001
	RF	-.245 .118	.101 .523	.084 .596	1	-.098 .536	.110 .488
	CRP	.355* .021	.196 .213	.602** .000	-.098 .536	1	.458** .002
	P53	-.006 .969	-.112 .482	.512** .001	.110 .488	.458** .002	1



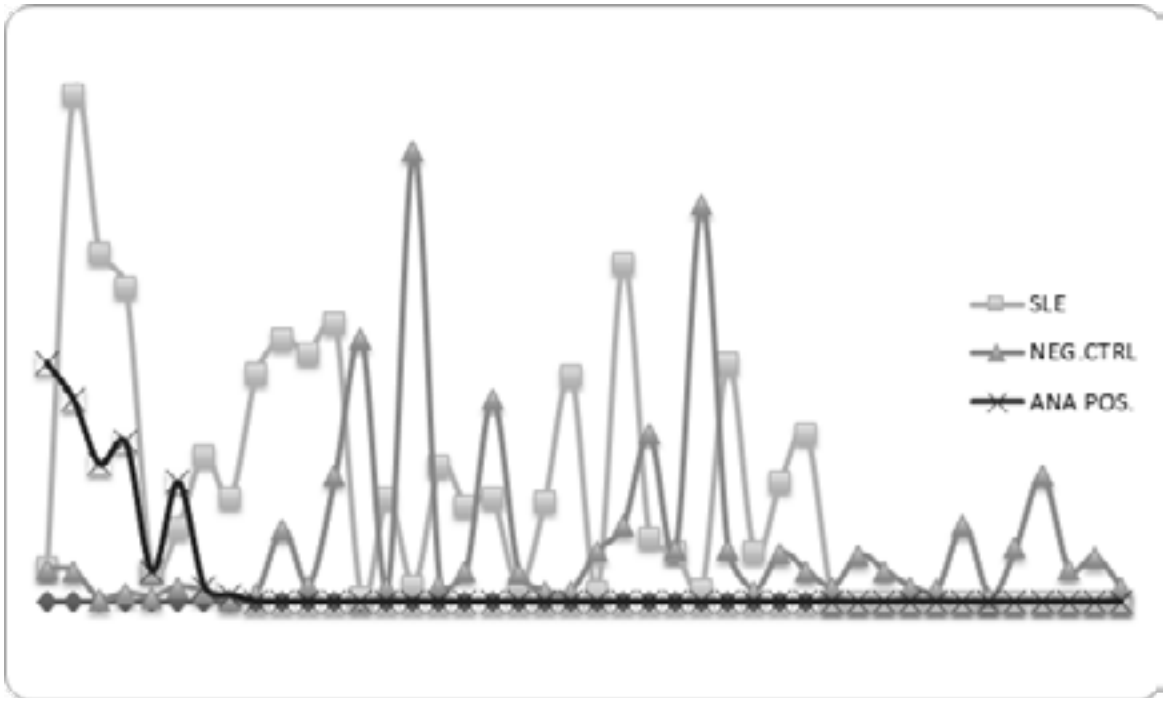


Figure 1:
(A)Line plot of serum ferritin levels in the three groups
(B)Line plot of serum p53 levels in the three groups

DISCUSSION

This study investigated the serum levels of ferritin, total IgE, P53, RF and CRP in systemic lupus erythematosus (SLE) patients, which is reportedly becoming a common systemic autoimmune disease in Sub-Saharan countries like Nigeria (1). The observed female gender preponderance for SLE in our study population may be due to sex hormone modulation of SLE, which predisposes to the formation of autoantibodies in women, thereby causing clinically apparent SLE. This observation is in concordance with previous studies in Caucasian populations that reported a higher incidence of SLE in female gender compared to their male counterpart (14), and other studies that reported increased inflammatory cytokines in human cells after exposure to Oestrogen (15). However, progesterone hormone increase was associated with reduced cytokine activity (16). Furthermore, the extra X-chromosome in the female gene has been reportedly linked to SLE onset (16-18). However, the ratio of incidence in females to males in our study (4:1) differs from 9:1 reported by Danchenko et al. [3] and 4-12:1 by Dall'Era (19). This variation could be attributed to population differences and other clinical factors that may have been modified by environmental factors or geographical peculiarities. In addition, the use of estrogen-containing contraceptive agents, which is associated with a 50% increase in risk of developing SLE, and the administration of estrogen to postmenopausal women, which doubles the risk of SLE, is not as common among the females in our environment compared to Caucasian population (17, 18).

Age has been previously linked with the incidence of SLE in males predisposed to older or advanced age compared to females (20). However, recent studies have reported that diagnostic delay and misdiagnosis may be responsible for the association of SLE with advancement in age (21). Our study observed an onset within early and late middle age in male (33.83) and female (34.71) participants. This is in range with the findings of Adelowo and Oguntona (22), who reported SLE patient's mean age as 33 years, while Rus et al. (23) reported a median age of 15-44 for black females and 45-64 for black males at diagnosis.

Interestingly, we observed a positive correlation between serum total IgE levels and age, with the levels increasing with age in the SLE group owing to a probable decline in the immune system. The serum total IgE levels in the male participants were observed to increase compared to those in the female participants. Increased IgE levels in males compared to females and positive correlation with age observed agree with Sekigawa et al. (24), which showed elevated IgE levels in male SLE participants compared to female participants. However, the increase in IgE aging males' interplay with increasing incidence of SLE and its clinical importance should be elucidated. Total IgE levels are influenced by genetic makeup, race, immune status, and environmental factors (25). In agreement with our findings, elevated serum IgE has been described in SLE. However, the study by Parks et al. (11) provides limited evidence of a direct association between total serum IgE and SLE overall or with other disease characteristics after adjusting for demographic characteristics and allergy history. Some authors have postulated that IgE is not implicated in connective tissue disease, while others claim that IgE plays an essential role in the disorder (9, 25). However, the increase in total IgE levels and its association with age, as observed in our study, may be important in the progressive decline in almost all system and organ functions reported in an aging population (26). Aging affects the immune system significantly in a process defined as "immunosenescence" (27, 28). The functional hematopoietic potential is maintained under basal conditions; however, stem cell renewal and production of downstream functional blood cells are gradually impaired with aging, resulting in myeloid malignancies, anemia, and immune dysfunction (28). Generally, reduced antibody production and impaired dendritic cell activity are present in elderly participants (29). In the study by De Amici and Ciprandi (30), the observed levels of total IgE were increased with age. He reported that there was an increasing trend during aging, with a peak in the oldest subgroup (85 years). A possible explanation for this observation may

be that an impaired regulatory function occurs during senescence, making it not unusual to detect autoantibodies in elderly participants.

High serum ferritin levels have also been reported in patients with active SLE compared to inactive SLE (31). By this finding, we reported markedly elevated serum ferritin in the SLE cases for the first time in our study population compared with the ANA-positive case and control groups, p-value < 0.05 (0.001). Ferritin is an acute-phase protein and is elevated in inflammatory reactions such as SLE. Serum ferritin concentration results from the leakage of tissue ferritin, an intracellular iron storage protein. It differs slightly from tissue ferritin and contains little or no iron (32). The level of ferritin in plasma represents the balance between its secretion, which is directly related to intracellular iron synthesis, and its clearance, mainly in the liver and other organs Kalantar-Zadeh et al. (33). However, liver dysfunction and inflammatory factors may interfere with the synthesis and clearance of ferritin, thereby increasing serum ferritin levels due to circumstances not related to iron metabolism Wirwood (32). In agreement with our study, Varnasa et al. (5) reported that the expression of ferritin was increased in SLE patients compared to control participants in their study population.

Interestingly, we also observed an increase in p53 in our case compared with controls. The p53 is a tumour suppressor protein that controls cell cycle activity leading to apoptosis of autoreactive cells. This event prevents aberrant cells' proliferation and differentiation and susceptibility to cancer development (6-7, 34). Therefore, any mutation in the p53 gene can cause cancer and autoimmune diseases (8, 35-36). A study by Nabavi et al [37] showed that some signs and symptoms of lupus were significantly correlated with p53. Another study employed genetic network analysis and Bayesian statistics to identify noteworthy genetic variants having strong interaction with SLE. Some of the genes identified include TP53, NFKB1, IL6, STAT, JAK2, RANTES amongst others, suggesting the possible involvement of p53 protein in SLE pathogenesis (38). The P53 protein levels are low in normal cells and are kept low through its continuous degradation, which mechanism may be deficient in SLE. Thus, DNA damage in SLE may trigger the increase of p53 proteins, subsequently stopping the cell cycle. In agreement with the observation of Nabavi et al. (37), our study reports an increase in serum p53 levels in both SLE and ANA-positive cases compared to control groups, although the increase was more pronounced in the SLE group. This may be explained by the fact that the p53 protein is a short-lived transcription factor expressed at low concentrations in normal cells and is maintained at low levels by continuous degradation in the ubiquitin-proteasome proteolytic system (36, 39). This mechanism may be deficient in SLE. Upregulation of p53 is paramount to damaged, cancerous, and inflamed tissues. Some of the mechanisms associated with p53 activation include increased transcription, increased intra-nuclear accumulation of active p53, down-regulation of Mdm2-Mdmx, which usually represses chromatin-bound-p53, various downstream post-translational modifications of both p53 and its regulators, including Mdm2; and raised cytosolic p53 (40). Any of these may be responsible for the increased p53 protein in SLE reported in our study. Furthermore, a positive correlation was found between ferritin and p53 levels. This was observed in the Negative Control cases but lost in both the SLE and ANA positive controls. Ferritin as an acute phase protein did not increase in the control cases as expected in apparently normal participants. The p53 protein did not increase in this group as normal cell cycle and apoptosis were properly regulated in these participants by the p53 protein (39). However, the levels of p53 were increased in both the SLE and ANA-positive control cases, while the increase in ferritin was not significant in ANA-positive cases. The increase in both ferritin and p53 was highly pronounced in SLE cases. Increased p53 protein may contribute to enhanced serum ferritin levels. A study by Zhang et al. [40] reported increased H and L subunits of ferritin protein following p53 induction in lung cancer cells. They established that p53 might additionally initiate tumor suppression and apoptosis via post-translational modification of iron by inducing ferritin and repressing

transferrin receptor 1 (TfR1) (40). Furthermore, Lee et al. (41) reported a direct link between ferritin and p53 protein, which also controls oxidative stress. An immunoprecipitation assay demonstrated a direct binding of p53 to both H- and L- ferritin in HEK293T cells. This binding to ferritin activated p53, which was indicated by an enhanced reporter activity of p53 after binding. This p53 activation is independent of the ferroxidase activity of ferritin, but in cells with H- ferritin down-regulation, it is sharply repressed Lee et al. (41). It was also shown that the expression level of H-ferritin was regulated by p53, a process mediated by the multiprotein complex Bbf and the trimeric transcription factor NF-Y (42). This study established a well-delineated feedback loop between p53 and ferritin, underscoring ferritin's potential in cancer therapy Min Pang and Connor (43). The differential pronounced increase of ferritin in SLE and the increase in both ferritin and p53 in SLE and ANA may be a promising differential diagnosis and monitoring biomarker for SLE and ANA-positive cases in our study population.

Rheumatoid factors are found in people with rheumatoid arthritis, which is estimated to affect 0.5 to 1% of the population worldwide and 2 to 3 times more common in females than in males. The concentration of rheumatoid factors tends to be highest when the disease peaks and decreases during prolonged remission. Conversely, failure to find RF does not rule out rheumatoid arthritis because up to 20% of people with this disorder produce no RF or have it at very low levels (44). In this study, however, there was no significant difference in the serum levels of RF in the three groups, p-value >0.05(0.153). About 24% of participants in the control group and 50% of participants in the ANA-positive control group were found to have positive RF. This finding was also observed in the SLE cases, as 33.3% of the females had positive RF antibodies. This agrees with several reports that positive RF test results may also be seen in healthy people and people with chronic inflammatory processes, infectious diseases, and autoimmune diseases such as SLE, and that some people produce RF in the absence of any disease, particularly in old age (45-47). However, 73.3% of participants in the SLE case group had Negative RF. This further showed that the manifestation of SLE is not exclusive to the presence or absence of RF antibodies. However, the antinuclear antibodies found in the ANA-positive control cases may result from the presence of RF antibodies since 50% of ANA had positive RF values.

C-reactive protein (CRP) is implicated in several pathological pathways, including chronic inflammatory disorders. The finding is non-specific, as the elevation can be expected in virtually all diseases involving tissue damage (46). The sudden rise, however, does indicate an inflammatory process. It is secreted during an acute phase response influenced by the cytokines involved in the inflammatory processes. C-reactive protein activates the complement pathway that is affected in individuals with lupus. It correlates with disease activity in people with a variety of rheumatic diseases, including RA and inflammatory arthritis. However, for reasons that are not clear, CRP levels in individuals with lupus in our study are only modestly but insignificantly elevated. This is probably because the autoimmune process fails to stimulate a normal acute phase response in SLE, and CRP is not increased (48). Like other inflammatory markers, CRP increases in acute inflammation but does not rise in lupus unless an infection occurs. Tan et al. (49) reported that CRP remains low despite high disease activity in SLE as these patients have circulating autoantibodies with monomeric levels of these antibodies correlated with disease activity. Figueredo et al. (50) have also reported that SLE patients with higher CRP and anti-CRP antibodies showed increased frequencies of anti-dsDNA antibodies compared to those without Figueredo et al. (50). However, this claim was not observed in this study.

A correlation between ferritin and CRP levels was also observed in the control group. However, this correlation was sustained in the SLE cases but was not found in the ANA-positive control group, probably because the antinuclear antibodies failed to stimulate a normal acute phase response in these subjects, and CRP was not elevated. Similarly, CRP

and p53 levels were also found to be correlated in the control group and the ANA-positive controls. This correlation was, however, not seen in the SLE cases. A normal acute phase response fails to be stimulated by the autoimmune process in SLE, and CRP is not increased (48), even though there is an elevation in the p53 levels in these participants. This observation may be due to the presence of the anti-dsDNA antibodies in SLE. There was also a strong negative correlation between the levels of ferritin and RF. This correlation was activated in the SLE cases but was lost in the Control and ANA-positive control cases. This shows that the increase in ferritin levels in SLE was not because of RF antibodies but due to the presence of anti-dsDNA antibodies. This dynamics pattern in the relationship between these parameters in cases (SLE and ANA) and controls shows promising differential diagnostic tools and probably prognostic markers.

Furthermore, in concordance with the study by Beyan et al. (39), serum ferritin levels in SLE patients were higher than in RA patients. Also, Age correlated with total IgE and CRP levels. The correlation between Total IgE and age was observed in the SLE cases. The levels were increased in the elderly SLE participants. This may be partly due to immunosenescence in the elderly and high levels of p53, which may accelerate the aging process through excessive apoptosis. However, the correlation between CRP and age observed in the ANA-positive case group in our study population does not agree with the study of Friedman and Young (46), which reported an identical level of CRP in both men and women but was not correlated with age. Although it is possible that the presence of antinuclear antibodies in the serum of these participants resulted in this correlation, it was consistent and emphasized our hypothesis that environmental and geographical factors play important roles in the variation of different populations.

CONCLUSION

This study uncovers the pivotal role of p53 and dysregulation of the cell cycle, revealing an intriguing interplay that suggests a relationship between the processes of inflammation and apoptosis in SLE patients. The study also confirms the higher prevalence of SLE in females, albeit at a lower rate in our study population compared to published data from the Caucasian population. Importantly, this study is the first to report increased serum levels of ferritin and p53 in SLE in our study population. The presence of antinuclear antibodies in the serum is associated with elevated ferritin and p53 levels, regardless of age and sex. Furthermore, a strong positive correlation was observed between increased serum ferritin and elevated p53. This study therefore establishes a relationship between the processes of inflammation and apoptosis in SLE. Additionally, serum total IgE levels were not significantly different in the three groups but were clearly influenced by both sex and age. Moreover, the serum levels of RF and CRP were not elevated in SLE, indicating that they are not specific to SLE. However, the correlation with the acute phase protein, ferritin, and the cell cycle regulator, p53, demonstrated an interesting interplay and relationship, which could be explored in the diagnosis and management of the disease. Notably, the dynamic differences and correlations in the cell cycle regulator (apoptosis) and acute phase proteins and inflammatory markers investigated in this study present promising differential diagnostic tools and potentially prognostic markers for the management of Systemic lupus erythematosus, highlighting the practical implications of our findings.

Authors' contributions

OA and NNO conceptualized the study, which OA designed and supervised. NNO, LAP, and KMA conducted the study and collected relevant data for the article. NNO and TAS did the literature review and produced the initial draft of the manuscript. All authors contributed to interpreting the data, structuring, and writing the article. All authors approved the final version and take full responsibility for all its parts.

Declaration of Conflict of Interest

The authors declare that the research has no

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