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Association between Interleukin-21 Serum Level and IL-21 Genetic Polymorphism with the Cardiovascular Morbidity Risk in Rheumatoid Arthritis and Systemic Lupus Erythematosus Patients

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ABSTRACT

Background: In cases with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), attention should be given to the risk of cardiovascular diseases, which are responsible for an excess burden of morbidity & mortality. In cases with RA and SLE, the cardiovascular system (CVS) should be evaluated for early detection of subclinical cardiovascular affection.

Objective: To assess serum interleukin-21 level and IL-21 genetic polymorphism association with the CVS risk in cases with RA and SLE.

Patients and methods: Seventy patients with RA, seventy patients with SLE and seventy matched controls were included in the study. Measurements of serum IL-21 levels were conducted by using ELISA procedure, and polymerase chain reaction (RT-PCR) was used to determine the genotypes. Cardiovascular assessment was done by: electrocardiography, transthoracic echocardiography, evaluation of carotid atherosclerosis by intima media thickness (IMT) of the carotid artery and evaluation of endothelial function by flow mediated dilation (ED-FMD) of the brachial artery.

Results: Serum interleukin-21 level was significantly higher in cases compared to healthy controls (HC), with significant elevation in clinically active patients. A significant relationship between serum IL-21 level with activity score, ejection fraction, intima media thickness, cholesterol, low density lipoprotein (LDL) and flow mediated dilatation was found. Patients with rs6822844 GT and TT haplotypes showed higher frequency of subclinical cardiovascular abnormalities in RA (p=0.0002, 0.01) and in SLE (p=0.001, 0.025) patients' groups respectively.

Conclusion: IL-21 may be a potential biomarker of cardiovascular risk in RA and SLE, and could be used as a possible target for new therapeutic agents. IL-21 polymorphism was significantly accompanied by inherited predisposition to RA and SLE and their associated cardiovascular morbidity.

Keywords: Rheumatoid Arthritis, Systemic Lupus Erythematosus**,** Interleukin-21, Cardiovascular risk.

INTRODUCTION

The autoimmune disorders (AID) RA and SLE are typified by persistent, systemic inflammation that affects many joints. Larger joints are impacted after the smaller joints in the hands and feet [(1)].

Infection and other systemic comorbidities are frequently the cause of increased mortality in RA and SLE, cardiovascular and pulmonary diseases. The mortality for cardiovascular diseases (CVDs) accounts for between one third and one half of RA and SLE deaths [(2,3)].

Attention should be given to the risk of CVD for early detection of subclinical cardiac risk in asymptomatic RA and SLE patients for adequate treatment that may limit long-term morbidity and mortality in these patients [(4)].

The key players in inflammation are cytokines, which control immune cell division, proliferation, maintenance, and apoptosis [(5)].

One of the cytokines that has recently been studied in the pathophysiology of several autoimmune disorders is IL-21. Numerous investigations indicate that IL-21 polymorphisms predispose a person to autoimmunity [(6)]. Targeting interleukins may be a particularly successful strategy for treating pressure overload since they are identified to play a significant function in terms of myocardial remodeling [(7)].

T follicular helper (Tfh), Th17, and activated CD4+ T cells all naturally generate IL-21, a new class I cytokine [(8)]. Numerous immune-regulatory activities of IL-21 include controlling T cell proliferation, boosting the stimulation and proliferation of natural killer cells, and differentiating B cells into plasma and memory cells, which raises the production of antibodies [(9)].

Certain polymorphisms in the IL-21 gene are discovered to be accompanied by several inflammatory and autoimmune disorders, comprising RA, SLE, and inflammatory bowel disease [(10)].

This suggests that these disorders are predisposed to one another genetically [(10)]. According to recent reports, individuals who have suffered myocardial infarction and have elevated blood IL-21 levels are at risk of developing heart failure [(11)].

While external delivery of recombinant IL-21 protein increases cardiac cell damage, endogenous IL-21 neutralization protects against myocardial injury and decreases inflammation and apoptosis degrees. Though its precise function in myocardial remodeling

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is still unclear, IL-21 seems to be a promising new biomarker for myocardial damage [12].

The objective of this work was to assess serum interleukin-21 level and IL-21 genetic polymorphism association with the cardiovascular risk in cases with RA and SLE.

PATIENTS AND METHODS

This study was conducted on seventy patients with RA fulfilled the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) 2010 criteria for diagnosis of RA [13], seventy SLE patients fulfilled the classification criteria of SLE international collaborating clinics (SLICC) [14] selected from the outpatient clinics of Rheumatology, Physical Medicine and Rehabilitation Department, Tanta University Hospitals, and seventy apparent healthy volunteers matching with patients in age and sex.

Exclusion criteria: We excluded patients with history of atherosclerosis, dyslipidemia, smoking or known previous CVD, and patients with chronic diseases that affect lipid profile as DM, hypothyroidism, liver or kidney disease, obesity. Pregnant and lactating women also were ruled out.

Assessment of the study subjects:

- **Clinical assessment:**

All patients were assessed clinically by: age, gender, disease duration, detailed history, and clinical examination, disease activity assessment using RA Disease Activity Score (DAS-28) or SLE Disease Activity Index (SLEDAI) [15,16], Functional assessment: By Modified Health Assessment Questionnaire (MHAQ) [17].

- **Laboratory assessment:**

Routine laboratory investigations were conducted, which included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), and lipid profile: Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and LDL-C.

RA patients: Rheumatoid factor (RF), anti-CCP.

SLE patients: Antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) levels.

Serum IL-21 level was measured using ELISA technique, and genotyped by RT-PCR to detect polymorphisms of IL-21 for patients and controls.

- **Cardiovascular assessment:**
  By electrocardiography (ECG), transthoracic echocardiography, evaluation of carotid atherosclerosis by IMT of the carotid artery and assessment of ED-FMD of the brachial artery.

Ethics approval:
Tanta University Faculty of Medicine's local Ethics Committee gave the project approval No. 36264. Every patient provided written informed permission, and the study was conducted in agreement with the guidelines outlined in the Declaration of Helsinki.

Statistical analysis

IBM SPSS statistics version 20.0 was utilized to conduct the statistical analysis. The range, mean±SD used to depict continuous data. Numbers and percentages were used to depict the qualitative data. The t-test was utilized to compare continuous data between groups, while the X^2-test was employed to evaluate qualitative data between several groups. A Pearson correlation analysis was conducted among the variables. $P < 0.05$ was used as the significance threshold.

RESULTS

The study included seventy patients in group 1 (RA), their age ranged from 29 to 60 years with a mean of 42.73 ± 9.89 years, seventy patients in group 2 (SLE), their age ranged from 24 to 65 years with a mean of 46.03 + 11.96 years, regarding gender; most of the patients were females in both groups (Table 1). The age of control group ranged from 25 to 59 years with a mean of 41.40 ± 10.61 years, 63 (90%) were females and 7 (10%) were males. There was no significant difference between the patients and control groups with regard to age and gender (0.624, 0.424 respectively).

Table (1): Clinical and laboratory data of the study subjects:

Parameters	Rheumatoid arthritis (n= 70)	Parameters	Systemic Lupus Erythematosus (n= 70)
Age (years)	42.73±9.89(29-60)	**Age (years)**	46.03+11.96(24-65)
DD (years)	10.06 ± 7.96 (1-33)	**DD (years)**	10.02± 6.72(2-31)
Gender F/M	67(95.71%)/3(4.29%)	**Gender F/M**	65(92.86%)/ 5(7.14%)
DAS28 score	5.73 ± 1.49	**SLEDAI**	13.30± 3.95
MHAQ	0.68 ± 0.16	**MHAQ**	1.05 ± 0.24
Hemoglobin (g/dl)	11.28 ± 1.27	**Hemoglobin (g/dl)**	11.58±1.63
ESR (mm/1st h)	37.6±7.2	**ESR (mm/1st h)**	27.8 ± 5.2
CRP (mg/mL)	18.9±4.5	**CRP (mg/mL)**	14.19 ± 3.4
RF positive (%)	46 (65.7%)	**ANA positive (%)**	70 (100%)
Anti-CCP positive (%)	42 (60%)	**Anti-dsDNA positive (%)**	56 (80%)
TC (mg/dL)	202.68 ± 33.68	**TC (mg/dL)**	177.15±17.02
TG (ng/mL)	159.78 ± 39.58	**TG (ng/mL)**	131.05 ± 29.96
LDL – C (mg/dL)	162.20 ± 35.57	**LDL – C (mg/dL)**	173.47 ± 41.76
HDL – C (mg/dL)	39.20 ± 7.27	**HDL – C (mg/dL)**	44.83 ±5.95
Abnormal ECG	14 (20%)	**Abnormal ECG**	13 (18.57%)
EF (%)	63.31 ± 7.43	**EF (%)**	65.19± 3.88
IMT	0.89± 0.19	**IMT**	0.90± 0.09
(ED – FMD)	6.41 ± 4.58	**(ED – FMD)**	8.69± 4.68
Treatment	Methotrexate 56%	**Treatment**	Glucocorticoids 65%
	Leflunomide 46%		Azathioprine 21.5%
	Hydroquine 55%		Hydroquine 73%
	Glucocorticoids 46%		NSAIDS 18%
	Biological 18%		Cyclophosphamide 15%

F: Female, M: Male, DD: Disease duration, DAS: Disease activity score, SLEDAI: SLE disease activity index, MHAQ: Modified health assessment questionnaire, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide antibodies, ANA: Antinuclear antibodies, anti-dsDNA: Anti-double-stranded DNA, TC: Total cholesterol, TG: Triglyceride, LDL-C: Low-density lipid cholesterol, HDL – C: High density lipid cholesterol, IMT: Intima media thickness of the carotid artery, ED–FMD: Endothelial dependent flow mediated dilatation, NSAIDS: Non-steroidal anti-inflammatory drugs.

Serum interleukin-21 level was accompanied by a significant increase in RA and SLE cases compared to healthy controls (HC). RA and SLE patients with high activity score were accompanied by a significant increase in serum IL-21 levels than those with lower score in both patient groups, as demonstrated in table 2.

Table (2): Serum Interleukin-21 level in different study subjects:

	Serum Interleukin-21 level (pg/mL)		p-value
Patients vs controls	274.5± 68.4	103.33± 25.6	0.001*
RA vs SLE	306.25 ± 75.9	242.75 ±60.4	0.06
Active vs inactive RA	420± 33.6	200± 21.8	0.03*
Active vs inactive SLE	354± 49.8	160± 40.0	0.04*

*Significant

There was a significant positive relationship between serum IL-21 level with activity score, TC, LDL, ejection fraction and intima media thickness, and a significant negative correlation with flow mediated dilatation, as demonstrated in table 3.

Table (3): Relationship between IL-21 serum levels and clinical, laboratory and cardiovascular manifestations of the study subjects:

Parameters	Serum Interleukin-21 level	
	r	p-value
Age (years)	0.164	0.212
DD (years)	0.206	0.115
Activity score	0.316	**0.015***
ESR (mm at 1st hour)	0.221	0.090
CRP (mg/mL)	0.025	0.850
MHAQ	0.157	0.232
Hemoglobin (g/dl)	-0.018	0.892
TC (mg/dL)	0.325	**0.011***
TG (ng/mL)	0.010	0.940
LDL – C (mg/dL)	0.357	**0.005***
HDL – C (mg/dL)	-0.028	0.834
Abnormal ECG	0.104	0.428
EF (%)	0.266	**0.042***
IMT	0.340	**0.008***
ED – FMD	-0.308	**0.017***
IL-21SNP	0.118	0.371

*Significant; SNP: single nucleotide polymorphism.

There was a significant difference between our patients and controls as regard IL-21 rs6822844 polymorphism genotypes as demonstrated in table 4.

Table (4): Genotype frequencies of IL-21 R polymorphism in patients and controls:

Polymorphism SNP			Patients (140)	Controls (70)	P-value
rs6822844	Genotypes	GG	25	11	0.007*
		GT	88	39	0.005*
		TT	27	20	0.011*

The heterozygous G/T type was the prevalent genotype in the patient group with subclinical cardiovascular abnormalities in RA and SLE patients (55.7% and 50% respectively), with significant difference was determined between the patients' groups with and without cardiovascular abnormalities regarding heterozygous GT and homozygous TT genotypes distribution in RA and SLE patients (Table 5).

The ratio of G and T alleles was much higher in RA and SLE patients with subclinical cardiovascular abnormalities than those patients without cardiovascular abnormalities, with no significant difference as demonstrated in table 5.

Table (5): Genotype distribution of IL-21 rs6822844 single nucleotide polymorphism among RA and SLE patients with and without subclinical cardiovascular abnormalities:

rs6822844	Subclinical cardiovascular abnormalities					
	RA patients (N= 70)		p-value	SLE patients (N= 70)		p-value
	+ve 46 (65.7%)	-ve 24 (34.3%)		+ve 54 (77.1%)	-ve 16 (22.9 %)	
Genotypes						
GG	3 (4.3%)	5 (7.15%)	0.11	14 (20%)	3 (4.3%)	0.79
GT	39 (55.7%)	9 (12.85%)	0.0002*	35 (50%)	5 (7.15%)	0.001*
TT	4 (5.7%)	10 (14.3%)	0.01*	5 (7.15%)	8 (11.4%)	0.025*
Alleles						
G	45 (32.1%)	19 (13.6%)	0.064	63 (45%)	11 (7.9%)	0.055
T	47 (33.6%)	29 (20.7%)	0.39	45 (32.1%)	21 (15%)	0.09

*Significant

DISCUSSION

Immune system cells release cytokines, some of which have excitatory functions and others inhibitory ones. Immune homeostasis depends on the maintenance of Th1/Th2 equilibrium, and disrupting this balance is thought to be the root cause of many autoimmune disorders. Numerous significant Th1 and Th2 cytokines, including IL-12, IL-4, IL-10, and IL-6, are implicated in the pathophysiology of AID [(18)].

Several researches recommended that IL-21, an inflammatory cytokine formed by follicular T cells, could have an essential function in terms of the onset and maintenance of inflammatory disorders and chronic AID in humans, such as SLE. Additionally, IL-21 value was higher in SLE patients than in the control group [(19)].

Previous research has shown that autoimmune disorders are associated with elevated plasma values of IL-21. Changes in the IL-21 gene can result in changes to the IL-21 protein, which in turn can influence an individual's vulnerability to certain autoimmune disorders. Numerous studies have looked at the relationship between IL-21 polymorphisms and a propensity for RA and SLE development in various groups. There are many polymorphisms in the IL-21 gene that are linked to SLE and RA [(20)]. The majority of investigations looked into the role of the rs6822844 polymorphism in an attempt to identify a possible connection between RA and SLE susceptibility [(21)].

Maiti *et al.* [(22)] assessed the relationships between rs6822844 and SLE, type 1 diabetes mellitus, RA, celiac illness, and primary Sjögren's syndrome. The autoimmune disorders and rs6822844 have been linked by these authors .

Following myocardial infarction, there is an improvement in heart function and a higher survival probability when there is a decrease in IL-21 plasma levels. In terms of the underlying processes, it is discovered that a deficit of IL-21 causes the infarcted region to repair more quickly [(23)]. It is proposed that IL-21 is a crucial agent that controls the remodeling of the heart caused by pressure - load. After pressure overload, IL-21 inhibition improves left ventricular function by lowering cardiomyocyte apoptosis and inflammation [(12)].

In our study, RA and SLE cases were accompanied by significant increases in serum interleukin-21 compared to HC (P=0.001). RA and SLE cases with a high activity score were accompanied by significant increases in serum IL-21 levels compared to lower score in both patient groups (p value = 0.03, 0.04 respectively) (Table 2).

This was consistent with recent research that found RA cases to have considerably higher plasma values of IL-21 than HC [(19)]. In a similar vein, IL-21 values were greater in sick people than in HC in research on early-stage RA patients [(24)]. Another investigation discovered that SLE patients had considerably greater plasma soluble IL-21 levels than controls [(20)].

According to our study, the RA patient group with DAS 28 more than 5.1 had a considerably greater level of IL-21 than the other groups with lower disease activity and the HC. There was also a consistent elevation in IL-21 value in the patient group with higher disease activity [(21)]. Serum IL-21 levels were demonstrated to be considerably greater in SLE cases with a high activity index score in another investigation; these findings confirm the critical function of IL-21 in the immunopathogenesis of SLE and its participation in disease severity [(25)].

Sglunda *et al.* [(26)] showed no statistically significant change in serum IL-21 value between participants with early RA and HC, which contradicts our findings. Additionally, RA cases with higher disease activity and HC had similar amounts of IL-21.

Contrary to our findings, research discovered that SLE patients' blood IL-21 values were considerably lower than those of controls [(27)]. Another research demonstrated no change in IL-21 values between the patient and the HC groups. On the other hand, compared to controls and inactive patients, the authors discovered that active SLE patients had a noticeably greater amount of IL-21 [(28)]. The medication that may have an impact on the blood level of IL-21 or the varying research sample size can be used to explain the discrepancy in results.

We discovered a strong positive link between serum IL-21 levels and activity score, TC, LDL, ejection fraction, and intima media thickness, and a substantial negative correlation with flow-mediated dilatation (Table 3).

Researchers **Nakou *et al.*** [(28)] **and Wang *et al.*** [(29)] discovered a favorable relationship between blood IL-21 levels and SLEDAI values. Further investigation revealed a favorable relationship between IL-21 and DAS28 [(30)].

Research conducted on CAD patients found that the disease's severity, TC, and LDL-C were all positively connected with an elevated blood level of IL-21 in CAD cases. Elevated levels of TC and LDL-C have been linked to atherosclerosis, which in turn can lead to the development of CAD [(31)].

Major efforts were conducted to assess the relationship between RA and SLE propensity and IL-21 polymorphisms. The rs6822844 G/T polymorphism was reported to have a strong relationship with AID, such as RA and SLE, among the other polymorphisms [(32)].

This is in agreement with our study that found significant difference between our patients and controls as regard IL-21 rs6822844 polymorphism genotypes (Table 4).

Though this is presumably the 1st study to look into whether the IL-21 gene polymorphism is connected to subclinical cardiovascular abnormalities

in Egyptian patients with RA and SLE, the majority of research has focused on the rs6822844 polymorphism in an attempt to find a possible relationship with the susceptibility to autoimmune diseases.

In our study, the heterozygous G/T type was the prevalent genotype in the patient group with subclinical cardiovascular abnormalities in RA and SLE patients (55.7% and 50% respectively), with significant difference was determined between the patients' groups with and without cardiovascular abnormalities regarding heterozygous GT and homozygous TT genotypes distribution in RA (0.0002 and 0.01 respectively), and SLE (0.001and 0.025 respectively) patients (Table 5).

The ratio of G and T alleles was higher in RA and SLE cases with subclinical cardiovascular abnormalities than those patients without cardiovascular abnormalities, with no significant difference (Table 5).

According to a study conducted on the Chinese population, IL-21 plasma levels were considerably greater in those with the TT genotypes of both the rs2055979 and rs12508721 SNPs. Both SNPs' TT genotypes were linked to the worst case of dilated cardiomyopathy (DCM) ($p < 0.001$). The IL-21 gene may be a significant factor in the Chinese population's vulnerability to DCM, according to their suggestion [(33)].

This is consistent with the findings that demonstrate a new mechanism through which IL-21 triggers myocardial inflammatory processes, apoptosis (programmed single cell death), and fibrosis, which ultimately end in stress-induced myocardial remodeling via the TIMP4 and MMP-9 signaling pathways [(12)].

Contrary to our findings, a study that looked at patients with congestive heart failure demonstrated that IL-21 values were lower in these patients and had a negative correlation with cardiac function parameters, while having a positive correlation with myocardial remodeling parameters. This recommends that IL-21 may have a protective action on the heart in CHF patients [(34)].

Finally, it is discovered that cardiac dysfunction in mice is improved by blocking IL-21. We infer that lowering IL-21 considerably improves heart failure brought on by pressure overload. The effects of stress overload-induced cardiac inflammation, apoptosis, hypertrophy, and fibrosis are alleviated by inhibition of IL-21. It has been discovered that several autoimmune illnesses can be treated by inhibiting the IL-21/IL-21 receptor. [(35)].

CONCLUSION

SNP rs6822844 of IL-21 gene is accompanied by subclinical cardiovascular abnormalities in RA and SLE patients. The GT and TT haplotypes increased the risk of subclinical cardiovascular abnormalities. If established, such outcomes will help to improve cardiac function in autoimmune diseases. Further studies on larger scale should be done to properly interpret our results.

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