

# Vascular Reactivity of Adult-Onset Systemic Lupus Erythematosus Patients

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**ABSTRACT** **Background:** Cardiovascular disease (CVD) is more frequent in patients with systemic lupus erythematosus (SLE) compared with age- and sex-matched healthy subjects. SLE is an autoimmune disease that is more prevalent in women (9:1). Women tend to develop CVD in post-menopausal years; however, women with SLE may develop endothelial dysfunction and CVD at a younger age in the pre-menopausal years.

**Objectives:** To study the endothelial function of adult-onset SLE patients from the north of Israel (the Galilee region) and to determine whether modern management (including biological treatments) changes the risk of developing CVD.

**Methods:** Thirteen females with adult-onset SLE without renal involvement were recruited to this prospective study. Clinical parameters (age, height, body mass index [BMI]), laboratory parameters (C-reactive protein [CRP] and hemoglobin level), and vascular responsiveness (flow mediated diameter percent change [FMD%]) were evaluated and compared to 11 age-matched healthy females. Student's *t*-test was used to find differences between the two groups.

**Results:** No difference was observed in adult-onset SLE female patients and their age- and sex-matched controls with regard to age ( $42.1 \pm 11.8$  years vs.  $36.6 \pm 10.8$  years,  $P = \text{NS}$ ), BMI ( $25 \pm 1.8$  kg/m<sup>2</sup> vs.  $25 \pm 2.5$  kg/m<sup>2</sup>,  $P = \text{NS}$ ), and hemoglobin level ( $11.9 \pm 0.9$  gr% vs.  $12.7 \pm 1.2$  gr%,  $P = \text{NS}$ ). However, a significant difference was found in CRP ( $2.57 \pm 2.2$  mg vs.  $0.60 \pm 0.37$  mg,  $P = 0.001$ ), vascular responsiveness ( $0.94 \pm 6.6$  FMD% vs.  $9.2 \pm 8.1$  FMD%,  $P = 0.012$ ), and height ( $165.7 \pm 4.5$  cm vs.  $171.6 \pm 5.8$  cm,  $P = 0.009$ ).

**Conclusions:** Adult-onset SLE females had impaired endothelial function even though they were treated by modern protocols.

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**KEY WORDS:** endothelial function, flow mediated diameter percent change (FMD%), inflammation, systemic lupus erythematosus (SLE)

Previous studies found a 50-fold increased risk of acute myocardial infarction (AMI) in women with systemic lupus erythematosus (SLE) aged 35–44 years old [1,2]. A prospective study that followed 252,676 patients with SLE and 758,034 subjects without SLE from 2008 to 2014 (mean age 51 years, 89% women, 49% white) found that SLE patients had a higher prevalence of atherosclerotic cardiovascular disease (ASCVD). SLE was associated with a higher rate of CVD, coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (CVA) [3]. The association between SLE and ASCVD was more significant in younger ages. Men and women with SLE aged 20–29 years old had the greatest odds to develop ASCVD [4]. In addition, adult-onset SLE patients have endothelial dysfunction and tend to have short stature. In fact, systemic, long-standing inflammation could be the mechanism that leads to impaired vascular function and the short stature.

Vascular endothelial injury and endothelial dysfunction are considered early key events in the pre-clinical stage of atherosclerosis, before clinical events occur. Several studies have shown that patients with SLE have endothelial dysfunction [5], with activation of platelets and type 1 interferon with elevation of vascular adhesion molecules and deposition of complement factors on platelets, indicating a hypercoagulability state in patients with SLE.

Our aim was to study the vascular reactivity of adult-onset SLE in female patients who live in the Galilee (the northern part of Israel), and who are treated with an advanced medical therapy.

## PATIENTS AND METHODS

This prospective study included 13 consecutive adult-onset SLE patients without renal involvement. The study was approved by the internal review board of the medical center. All patients gave written informed consent. Padeh Medical Center is a regional governmental hospital. The medical center treats patients from the eastern part of the Galilee region, a region that covers agricultural area, and has little traffic or industry. The locale is considered to be a clean area with little air pollution.

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Activity score, length of disease duration, vascular responsiveness (using the brachial artery method to measure the endothelial function and flow mediated dilatation percent change [FMD%]), the inflammatory marker C-reactive protein (CRP), body mass index (BMI), anti-nuclear antibodies, double stranded DNA (ds-DNA), complement component 3 (C3), complement component 4 (C4) levels, anti-Sjögren's-syndrome-related antigen A (anti-SSA) and anti-Sjögren's syndrome type B antibodies (anti-SSB), anti-Smith (Anti-Sm) antibodies, small nuclear ribonucleoprotein (snRNP), anti-scleroderma 70 antibodies (Anti-Scl-70 antibodies) and anti-cyclic citrullinated peptide (anti CCP) were measured. Mann-Whitney test (a non-parametric test) was used to analyze the difference between patients and healthy controls.

### RESULTS

All of our patients were females, aged  $42.1 \pm 11.8$  years old, and all started to show clinical manifestations of SLE as adults. Eleven healthy age-matched females volunteered to participate as the control group.

Disease duration was  $6.7 \pm 5.9$  years, and in all of them the disease activity score was significant ( $30.7 \pm 11.1$ ).

The change in diameter of the brachial artery post hyperemia was significantly lower in SLE patients compared with healthy controls ( $0.003 \pm 0.02$  cm vs.  $0.03 \pm 0.02$  cm,  $P = 0.01$ ). The flow mediated diameter percent change (FMD%) was significantly inhibited in SLE patients compared with healthy controls ( $0.9 \pm 6.6\%$  vs.  $9.1 \pm 8.0\%$ ,  $P = 0.012$ ) [Table 1].

CRP levels were significantly higher in SLE patients compared to controls ( $2.57 \pm 2.2$  mg vs.  $0.60 \pm 0.3$  mg,  $P = 0.001$ ). No difference was observed in hemoglobin levels ( $11.9 \pm 0.88$  gr% vs.  $12.7 \pm 1.26$  gr%,  $P = \text{NS}$ ), nor in BMI ( $24.7 \pm 1.8$  vs.  $24.4 \pm 2.4$ ,  $P = \text{NS}$ ). However, a significant difference was found in height. Patients with SLE had a short stature ( $165.7 \pm 4.5$  cm vs.  $171.6 \pm 5.8$  cm,  $P = 0.009$ ), that is, they were 5.9 cm shorter compared to the healthy controls.

### DISCUSSION

Our main finding was that patients with adult-onset SLE had severe endothelial dysfunction, high levels of inflammation, and short stature.

They all were born and raised in the Galilee, an agricultural area with no air-pollution, with different ethnicity (half Arabs, half Jews).

Although coronary artery disease is the leading cause of death among women, it occurs mainly in post-menopausal women older than 55 years of age. Unlike the general population, in a series of female SLE patients who were followed from 1980 to 1993, 67% of the patients with CVD had their first disease event under the age of 55 years, most of them (18 of 22 women) were younger than 45 years. According to this series, the incidence of acute myocardial infarction (AMI) in females with SLE was 50 times greater than in women in the general population. Premature CVD is a major factor in mortality of SLE young females. Postmortem examinations of women who died from an AMI revealed a significant atherosclerosis [6]. Recent studies, published in 2019 showed similar results. A strong association between SLE and ASCVD was found, and it was most apparent in younger patients [3]. The most significant increase in ASCVD peaked in women aged 30–49 years old. SLE by itself was found to be an independent risk factor, not encountered in the traditional CVD risk factors [7].

Detection of coronary artery disease and myocardial disease in young women with SLE is quite difficult. Using cardiovascular magnetic resonance (CMR) with late gadolinium enhancement and stress perfusion sequences found that 80% of the women with SLE enrolled to the study (mean age  $45 \pm 14$  years old) had low to moderate disease activity. Cardiac involvement in women with SLE has atypical clinical symptoms, and using MRI could detect early cardiac involvement [8].

It is believed that the same mechanisms leading to atherosclerosis (chronic inflammation, oxidative stress, lack of nitric oxide, endothelial dysfunction) are the ones that cause immune dysregulation characteristic of lupus [9-11].

### ENDOTHELIAL FUNCTION AND VASCULAR INFLAMMATION

We found that our SLE patients had severe endothelial dysfunction compared with the healthy controls ( $0.94 \pm 6.6\%$  vs.  $9.2 \pm 8.1\%$ ,  $P = 0.01$ ). The endothelium is a key regulator of vascular homeostasis. It is believed that the chronic inflammation observed in SLE impairs endothelial integrity and function, thereby initiating a cascade of events that lead to atherosclerosis and ASCVD. Flow mediated diameter percent change (FMD%) is a noninvasive method that has been ap-

**Table 1.** Statistical analysis of the endothelial function of systemic lupus erythematosus patients

	Age, years	Height, cm	Body mass index	Flow mediated diameter percent change	C-reactive protein (mg)	Hemoglobin (gr%)
Patients	$42.1 \pm 11.8$	$165.7 \pm 4.5$	$25 \pm 1.8$	$0.94 \pm 6.6$	$2.57 \pm 2.2$	$11.9 \pm 0.9$
Healthy	$36.6 \pm 10.8$	$171.6 \pm 5.8$	$25 \pm 2.5$	$9.2 \pm 8.1$	$0.60 \pm 0.37$	$12.7 \pm 1.2$
P value	NS	0.009	NS	0.012	0.001	NS

proved by the American Heart Association as a tool to estimate non-invasively endothelial function [12]. This method, based on the brachial artery method, has been confirmed to be an early predictor of ASCVD in multiple studies and in different populations of human subjects, among them patients with CAD and patients with PAD or patients with type 1 and type 2 diabetes mellitus.

Most of the studies that evaluated vascular reactivity of patients with SLE found that SLE patients have an impaired endothelial function. Most of the published data shows that SLE patients have lower FMD% values compared with healthy controls [13]. Endothelial dysfunction represents a very early sign of vascular disease and a useful marker of CVD risk assessment. A meta-analysis of 25 case-controlled studies involving 1313 SLE patients without CVD and 1012 healthy controls found that SLE patients had endothelial dysfunction. Diabetes mellitus, high diastolic blood pressure, and renal involvement were associated with worse endothelial dysfunction in patients with SLE [14]. An inverse correlation was found between SLE activity score and endothelial function [15].

Inflammation is a fundamental process leading eventually to atherosclerosis and CVD [10,11]. Recently, a clinical study proved that blocking interleukin 1 $\beta$  (IL-1 $\beta$ ) by canakinumab (a monoclonal antibody against IL1 $\beta$ ) had a clinical beneficial effects on coronary artery disease and on atherosclerosis [16]. Type I interferons (Type I IFNs) are considered to be key factors in the pathogenesis of SLE, and have been suggested to mediate increased endothelial progenitor cells (EPCs) apoptosis and differentiation of circulating angiogenic cells to non-angiogenic cells (CACs). Type I IFNs promote proangiogenic molecules and downregulate interleukin 1 signaling pathways affect the inflammasome and promote interleukin 18 activation and inhibit interleukin 1 $\beta$ . They are associated with over-expression of vascular cell adhesion molecule 1 (VCAM-1) and endothelial micro-particles [17].

Platelets were also activated in patients with SLE, with deposition of C1q (a marker of platelet activation), attracting EPCs and directing them to damaged endothelial regions in the blood vessel [18].

#### SHORT STATURE, SLE, AND CVD

We found that our patients (all of them with adult-onset SLE) were 5.9 cm shorter compared with the healthy controls. There are no studies that have described the association between endothelial function and height in patients with adult-onset SLE. Childhood onset SLE is considered a more aggressive disease with multiple end-organ damage, and patients with SLE enter adult life with more co-morbidity and complications due to the long-term disease activity and side effects of the medications. Growth failure was considered unique to childhood onset SLE [19]. Patients with childhood SLE were 2.4 cm shorter than the adult-onset SLE patients. Females diagnosed between 11 and 13 years of age were at

greatest risk for reduced final height [16]. Disease onset at the period of maximum linear growth may predict shorter-than-expected stature in adulthood. However, no study examined the height of adult-onset SLE patients and compared it to healthy controls [19,20].

#### LIMITATIONS

Our patients were diagnosed only in adulthood, but the short stature and the severity of the vascular responsiveness may suggest a long-standing disease, that could have started even at childhood, but was undetected clinically in our patients.

#### CONCLUSIONS

Endothelial dysfunction in patients with SLE was first described 20 years ago, and even though there are now more advanced treatments, including biological treatments, all patients still present with endothelial dysfunction, a sign of future CVD.

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**Capsule**

**Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19**

Progressive respiratory failure is the primary cause of death in the coronavirus disease 2019 (COVID-19) pandemic. Despite widespread interest in the pathophysiology of the disease, relatively little is known about the associated morphologic and molecular changes in the peripheral lung of patients who die from COVID-19. **Achermann** and colleagues examined seven lungs obtained during autopsy from patients who died from COVID-19 and compared them with seven lungs obtained during autopsies from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A (H1N1) infection and ten age-matched, uninfected control lungs. The lungs were studied with the use of seven-color immunohistochemical analysis, micro-computed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression. In patients who died from COVID-19-

associated or influenza-associated respiratory failure, the histologic pattern in the peripheral lung was diffuse alveolar damage with perivascular T-cell infiltration. The lungs from patients with COVID-19 also showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with COVID-19 as in patients with influenza ( $P < 0.001$ ). In lungs from patients with COVID-19, the amount of new vessel growth, predominantly through a mechanism of intussusceptive angiogenesis, was 2.7 times as high as that in the lungs from patients with influenza ( $P < 0.001$ ).

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**Capsule**

**A highly polarized TH2 bladder response to infection promotes epithelial repair at the expense of preventing new infections**

Urinary tract infections (UTIs) typically evoke prompt and vigorous innate bladder immune responses, including extensive exfoliation of the epithelium. To explain the basis for the extraordinarily high recurrence rates of UTIs, **Wu** et al. examined adaptive immune responses in mouse bladders. The authors found that, following each bladder infection, a high T helper type 2 ( $T_H2$ )-skewed immune response directed at bladder re-epithelialization is observed, with limited capacity to clear infection. This response is initiated by a distinct subset of CD301b<sup>+</sup>OX40L<sup>+</sup> dendritic cells, which migrate into the

bladder epithelium after infection before trafficking to lymph nodes to preferentially activate  $T_H2$  cells. The bladder epithelial repair response is cumulative and aberrant as, after multiple infections, the epithelium was markedly thickened and bladder capacity was reduced relative to controls. Thus, recurrence of UTIs and associated bladder dysfunction are the outcome of the preferential focus of the adaptive immune response on epithelial repair at the expense of bacterial clearance.

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