

Journal of Diagnostic Medical Sonography

<http://jdm.sagepub.com/>

Role of Serum TNF α Level in Atherosclerosis in Egyptian Systemic Lupus Erythematosus Patients

Manal Menyawi, Mary Wadie Fawzy, Y. Y. Ojra, Olfat G. Shaker and Amr Edrees

Journal of Diagnostic Medical Sonography published online 17 September 2014

DOI: 10.1177/8756479314550313

The online version of this article can be found at:

<http://jdm.sagepub.com/content/early/2014/09/16/8756479314550313>

Published by:



<http://www.sagepublications.com>

On behalf of:



Society of Diagnostic
Medical Sonography

[Society of Diagnostic Medical Sonography](http://www.sdmsonography.org)

Additional services and information for *Journal of Diagnostic Medical Sonography* can be found at:

Email Alerts: <http://jdm.sagepub.com/cgi/alerts>

Subscriptions: <http://jdm.sagepub.com/subscriptions>


Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [OnlineFirst Version of Record](#) - Sep 17, 2014

[What is This?](#)

Role of Serum TNF α Level in Atherosclerosis in Egyptian Systemic Lupus Erythematosus Patients

Journal of Diagnostic Medical Sonography
1–6
© The Author(s) 2014
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8756479314550313
jdms.sagepub.com


Manal Menyawi, MD¹, Mary Wadie Fawzy, MD¹, Y. Y. Ojra⁴,
Olfat G. Shaker, MD², and Amr Edrees, MD³

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that principally affects women in their childbearing years. Many cytokines have been implicated in regulating disease activity and the involvement of different organs in patients with SLE. The study was conducted to determine serum tumor necrosis factor alpha (TNF α) levels in SLE patients and its relation to clinically active disease and to assess the possible role of serum TNF α level in atherosclerosis. Thirty Egyptian female patients with SLE and 15 matched healthy control subjects had serum TNF α levels measured. In addition, the relation of common carotid artery intima-media thickness (CIMT) to serum TNF α was evaluated. Mean serum TNF α level of SLE patients was 48.36 ± 58.27 pg/ml, significantly different from the control group (17.62 ± 16.63 pg/ml; $P = .014$). There was a statistically significant difference in right carotid CIMT between SLE patients (0.06 ± 0.01 cm) and the control group (0.054 ± 0.009 ; $P = .002$). There was also a statistically significant difference in left carotid CIMT between lupus nephritis patients (0.07 ± 0.01) and non-lupus nephritis patients (0.06 ± 0.01 ; $P = .027$). These data indicate the activation of immune response in SLE patients suggested by their high levels of TNF α . Increased CIMT in lupus patients was not related to TNF α and the lipid profile, suggesting an underlying etiology for atherosclerosis in lupus patients other than those factors. High CIMT in nephritis patients denote the role of nephritis in atherosclerosis.

Keywords

SLE, atherosclerosis, carotid intima media thickness

Introduction

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease with a broad range of clinical manifestations. Although the pathogenesis is believed to lie in the dysregulation of the immune system, the involvement of various organ systems often leads to secondary morbidities resulting in renal failure, hypertension, or central nervous system (CNS) disorders. More recently it has becoming increasingly clear that accelerated atherosclerosis associated with SLE may contribute to premature mortality.¹⁻³

Atherosclerosis has been shown to be enhanced in autoimmune diseases; noninvasive investigations show increases in intima-media thickness, carotid plaque, and coronary artery calcifications in patients with antiphospholipid syndrome (APS), SLE, and rheumatoid arthritis (RA) compared to controls.² Cytokines are master regulators of the innate and adaptive immune response and, unsurprisingly, are known to regulate and coordinate many stages of atherosclerosis. Many cytokines, such as

interleukin (IL)-1, IL-6, IL-10; interferon gamma (IFN γ); and tumor necrosis factor alpha (TNF α), are highly expressed in atherosclerotic regions and exhibit both pro- and anti-atherogenic actions.³ TNF α in particular has been shown to be both a proinflammatory and an immunoregulatory cytokine.⁴⁻⁸ The elevated circulating levels of TNF α found in SLE patients have been found to be associated with high triglyceride and low high density lipoprotein (HDL) levels.⁵

Carotid intima-media thickness (CIMT) measurements have increasingly been used in observational

¹Department of Internal Medicine, Cairo University, Giza, Egypt

²Department of Biochemistry, Cairo University, Giza, Egypt

³Department of Internal Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

⁴Department of Internal Medicine, Palestine Hospital, Palestine

Corresponding Author:

Mary Wadie Fawzy, MD, Department of Internal Medicine, Cairo University, 18 El Sherbiney Street, Dokki Giza, Giza 002, Egypt.
Email: drmarywadie@yahoo.com

and intervention studies.⁹⁻¹⁸ CIMT has been applied as an outcome variable in studies on the determinants of atherosclerosis, and it has been employed as an exposure variable in studies on the prognostic value of CIMT in order to predict coronary artery disease (CAD) and stroke. Changes in CIMT over time as a marker for atherosclerosis progression and possible change in cardiovascular risk have been used in intervention studies as a primary outcome variable aimed at assessing the effects of risk factor interventions. More recently, reports on the risk factors for progression of CIMT have become available from observational studies. The current widespread application of CIMT measurements has been based on the validity, standardization, and reproducibility of the measurement and the evidence an increased CIMT can be regarded as a marker of atherosclerosis and of increased cardiovascular risk. A number of these studies have specifically addressed SLE patients.¹⁵⁻¹⁷

Methods

Thirty consecutive female Egyptian SLE patients mean age 27.4 ± 8.7 years were chosen according to the American College of Rheumatology criteria¹⁹ from the outpatient rheumatology and immunological clinic. The local ethics committee of the Cairo University Faculty of Medicine approved the study, all patients were informed about the procedure, and a verbal consent was taken. Clinical activity was assessed at the time of venipuncture using the systemic lupus erythematosus disease activity index (SLEDAI). Fifteen age-matched healthy female control subjects from a similar ethnic background were also recruited and included in the study.

A full clinical history was obtained for all subjects, and laboratory testing was done to measure complete blood count, erythrocyte sedimentation rate, C-reactive protein, Complements C3 and C4, serum creatinine, serum cholesterol, serum triglyceride, low-density lipoprotein (LDL) and HDL cholesterol, urinalysis, 24-hour urinary protein, anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, and serum TNF α . In addition to the presence or absence of SLE, patients were further classified as to the presence or absence of dyslipidemia and lupus nephritis.

All subjects had bilateral carotid artery duplex sonography to measure the intima-media thickness of the distal common carotid as a single point measurement at the site of maximum thickness (Figure 1), assess for any atherosclerotic plaque, and record the peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI) of the internal carotid artery. Gray-scale imaging and spectral Doppler velocity measurements were done according to our standardized laboratory protocol using an HD5000 system with a 7.5 MHz probe (Philips Ultrasound, Bothel, Washington). The same operator interpreted all studies in a blinded fashion.

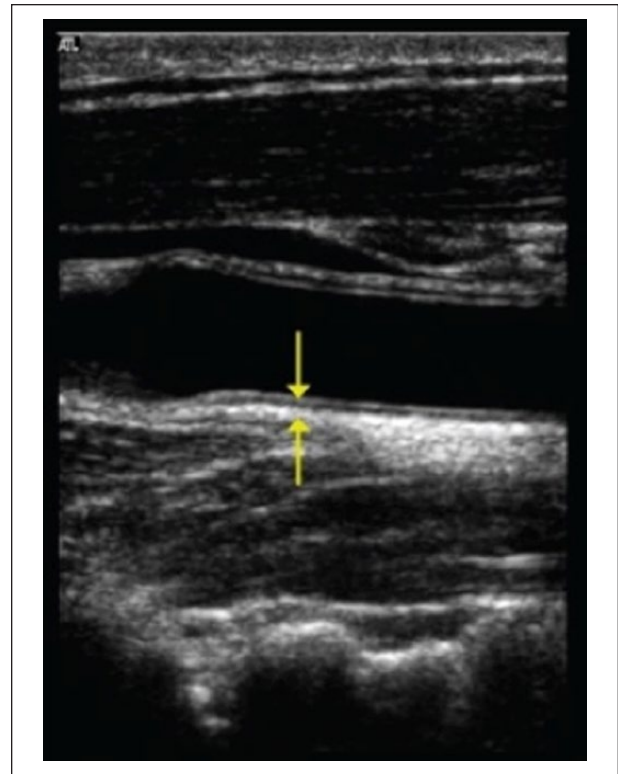


Figure 1. Sagittal gray-scale image of the distal common carotid artery showing the single point measurement technique for intima-media thickness.

The data were coded and analyzed using the statistical package SPSS, Version 15 (IBM, Cary, North Carolina). The data were summarized using descriptive statistics of mean, standard deviation, minimal and maximum values for continuous quantitative variables, and number and percentage for qualitative values. Statistical differences between groups were tested using the chi-square test for qualitative variables, independent sample Student *t* test for quantitative normally distributed variables, and the nonparametric Mann-Whitney test for quantitative variables, which were not normally distributed. Correlations were done to test for linear relations between variables. A *P* value of .05 was considered to indicate a significant difference between groups.

Results

Twelve of the 30 SLE patients presented with chronic dermatologic changes characteristic of discoid lupus. Clinical activity as indicated by the SLEDAI score ranged from 2 to 30, with a mean of 8.73 ± 7.45 . Anemia, defined as a hemoglobin below 12 gm/dl, was found in 22 patients (73.3%), with values ranging from 9.2 to 11.8 gm/dl. Leucopenia, a total leukocyte count below 4×10^3 cells/microl, was found in 6 patients (20%), ranging from 1.7 to 3.3×10^3 cells/microl. Thrombocytopenia, a platelet

Table 1. Laboratory Findings for Tumor Necrosis Factor Alpha (TNF α) and Lipid Levels for Systemic Lupus Erythematosus (SLE) Patients and Controls (mean \pm standard deviation).

	SLE Patients (N = 30)	Controls (N = 15)	P Value
TNF α (pg/ml)	48.4 \pm 58.3	17.6 \pm 16.6	.014
Total cholesterol (mg/dl)	206.2 \pm 59.9	173.4 \pm 19.6	.010
High-density lipoprotein (mg/dl)	45.5 \pm 5.8	44.9 \pm 6.3	.484
Low-density lipoprotein (mg/dl)	123.4 \pm 39.9	109.9 \pm 14.2	.105
Triglycerides (mg/dl)	165.5 \pm 104.9	83.3 \pm 30.9	.001

Table 2. Comparison of Duplex Sonography Findings for Systemic Lupus Erythematosus (SLE) Patients and Controls (mean \pm standard deviation).

	SLE Patients (N = 30)	Controls (N = 15)	P Value
Right CIMT (cm)	0.06 \pm 0.01	0.054 \pm 0.009	.002
Left CIMT (cm)	0.06 \pm 0.01	0.06 \pm 0.01	.127
Right PSV (cm/sec)	75.0 \pm 16.0	85.4 \pm 28.5	.207
Right EDV (cm/sec)	28.4 \pm 8.30	30.3 \pm 9.2	.157
Left PSV (cm/sec)	80.1 \pm 18.5	93.7 \pm 18.1	.024
Left EDV (cm/sec)	32.6 \pm 8.2	34.8 \pm 6.6	.382

Abbreviations: CIMT, carotid intima-media thickness; PSV, peak systolic velocity; EDV, end diastolic velocity.

count below 150×10^3 cells/microl, was present in only 1 patient (3.3%). Dyslipidemia was noted in 10 patients (33.3%) and lupus nephritis in 11 patients (36.7%).

TNF α and serum lipid measurements for SLE patients and controls are shown in Table 1. The mean serum TNF α level in patients with SLE was 48.4 ± 58.3 pg/ml, significantly higher than that found in the control group (17.6 ± 16.6 pg/ml; $P = .014$). There also was a significant difference in total serum cholesterol level and serum triglyceride level between SLE patients and controls, with higher levels in the patient group, as shown in the table. A significant difference was found in the right carotid artery intima-media thickness between SLE patients (0.06 ± 0.01 cm) and the control group (0.054 ± 0.009 ; $P = .002$) (Table 2). Left internal carotid artery peak systolic velocity was elevated in the control group compared to SLE patients, but no other significant differences were seen in any duplex sonography-derived parameters between the 2 groups.

For SLE patients, there was significant correlation between SLE activity index scores (SLEDAI) and total cholesterol level, low-density lipoprotein cholesterol levels, 24-hour urinary protein, erythrocyte sedimentation rate, C-reactive protein, Complement 3, and left carotid intima media thickness, as shown in Tables 3 and 4. However, there was no correlation between serum TNF α levels and any of the other laboratory findings or duplex sonography measurements. There were also no significant differences in serum TNF α levels between dyslipidemic SLE patients and non-dyslipidemic SLE patients (Table 5), nor for patients with and without lupus

Table 3. Correlation of Laboratory Test Findings With Systemic Lupus Erythematosus Activity Index Scores (SLEDAI) and Serum TNF α Levels in Patients.

	SLEDAI (P value)	TNF α (P value)
Total cholesterol (mg/dl)	.021	.392
High-density lipoprotein (mg/dl)	.806	.652
Low-density lipoprotein (mg/dl)	.050	.169
Triglycerides (mg/dl)	.730	.417
24-hour urinary protein (gm)	.007	.178
Erythrocyte sedimentation rate (mm/hr)	.026	.504
C-reactive protein (mg/L)	.027	.986
Complement 3 (mg/dl)	.001	.165
Complement 4 (mg/dl)	.451	.370
Anti-dsDNA	.346	.964

Abbreviations: TNF α , tumor necrosis factor alpha; anti-dsDNA, anti-double-strand deoxyribonucleic acid.

nephritis (Table 6). The left common carotid artery intima-media thickness was significantly larger in patients with lupus nephritis compared to those without (Table 6); no other duplex sonography measurements showed any significant differences when comparing dyslipidemic with non-dyslipidemic patients and patients with and without lupus nephritis.

Discussion

The tumor necrosis factor family of cytokines, originally characterized by their ability to induce tumor cell apoptosis

Table 4. Correlation of Duplex Sonography Measurements With Systemic Lupus Erythematosus Activity Index Scores (SLEDAI) and Serum TNF α Levels in Patients.

	SLEDAI (<i>P</i> value)	TNF α (<i>P</i> value)
Right CIMT (cm)	.761	.618
Left CIMT (cm)	.024	.710
Right PSV (cm/sec)	.611	.485
Right EDV (cm/sec)	.885	.075
Right RI	.830	.265
Left PSV (cm/sec)	.386	.595
Left EDV (cm/sec)	.522	.453
Left RI	.259	.151

Abbreviations: TNF α , tumor necrosis factor alpha; CIMT, carotid intima-media thickness; PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index.

and cachexia, are now considered central mediators of a broad range of biological activities. The first 2 of these factors identified were tumor necrosis factor (TNF, originally called TNF alpha) and lymphotoxin (LT) alpha. The activities of the TNF family are now known to encompass beneficial effects for the host in inflammation and in protective immune responses against a variety of infectious pathogens. TNF family members on the other hand also exert host-damaging effects in sepsis, tumor cachexia, and autoimmune diseases. In addition, the essential roles of the core members of the TNF superfamily, LT alpha, LT beta, TNF, and TNF superfamily member 14 (TNFSF14, or LIGHT), as well as their receptors, during the organogenesis of secondary lymphoid organs and the maintenance of the architecture of lymphatic tissues is beginning to be understood.²⁰

Autoimmune rheumatic diseases (AIRDs) are associated with higher rates of cardiovascular morbidity and mortality, primarily secondary to accelerated atherosclerosis. This phenomenon can be attributed to traditional risk factors for atherosclerosis and use of specific drugs, such as corticosteroids, but also might be the result of other autoimmune and inflammatory mechanisms that are aggravated in AIRDs.² SLE is an autoimmune disease characterized by a wide variety of autoantibodies, some of which are pathogenic. In recent years it has become more evident that the polyclonal B cell activation in SLE is T-cell dependent. Tumor necrosis factor (TNF alpha) is both a proinflammatory and an immunoregulatory cytokine and has differential effects on B cells, T cells, and dendritic cells, as well as on apoptosis, the process of programmed cell death. Understanding how the immune system integrates the pleiotropic properties of TNF alpha is a challenge, particularly so in diseases like SLE.⁶ Patients with SLE are known to be at high risk of cardiovascular disease (CVD), and TNF α has been implicated in the pathophysiological processes of both SLE and CVD.⁵

In this study, we assessed the relationship between serum TNF α level and markers of atherosclerotic vascular disease in SLE patients to highlight the different etiology of atherosclerosis in SLE patients and to demonstrate any early changes in the carotid arteries in SLE patients. The study showed a significant elevation in serum TNF α levels in SLE patients compared to an age- and ethnic-matched control population. This finding is in agreement with the results of Svenungsson et al that showed plasma concentrations of circulating TNF α higher in SLE patients with no cardiovascular symptoms compared to population controls.⁵ However, they further showed that in SLE patients with cardiovascular manifestations there was a strong positive correlation between TNF α levels and plasma triglycerides. The present study showed no significant correlation between serum TNF α levels and serum triglyceride levels in SLE patients, but this may be due to differences in patient selection as none of the patients in this study had overt signs or symptoms of cardiovascular disease.

Common carotid artery intima-media thickness has been shown to be a surrogate marker for atherosclerosis associated with cardiovascular risk factors and with cardiovascular outcomes.⁹⁻¹¹ Although measurement of intima-media thickness is promoted as a tool for cardiovascular risk assessment in primary prevention, the incremental predictive value of the intima-media thickness over and above the value of traditional cardiovascular risk factor assessment has been questioned.^{13,14} The present study showed a significant increase in right carotid intima-media thickness in SLE patients compared to the control groups, in agreement with Caccipaglia et al¹⁵ who concluded that patients with SLE, despite equivalent exposure to "traditional" cardiovascular risk factors, presented with a significantly higher mean intima-media thickness of the common carotid artery than healthy subjects.

Early atherosclerosis develops in more than one-third of SLE patients. The main risk factors of early disease are the conventional ones plus factors such as antiphospholipid antibodies, persistence of chronic inflammation, decreased glomerular filtration rate, and prednisolone therapy. Chronic inflammation, particularly the influence of lupus nephritis on the process of atherogenesis in SLE, may exacerbate other risk factors.¹⁶ Sazliyana et al have reported that aggressive treatment of severe LN and the use of cyclosporine A as a steroid-sparing agent may have protective effects against premature atherosclerosis.¹⁷ In the present study there was a significantly larger left carotid intima-media thickness in lupus nephritis patients than in lupus patients with no nephritis.

It is hypothesized that the elevated triglyceride levels that are prevalent in SLE patients are in part attributable to anti-lipoprotein lipase and that this lipid abnormality

Table 5. Results of TNF α Levels and Duplex Sonography Findings (mean \pm standard deviation) for Systemic Lupus Erythematosus (SLE) Patients With and Without Dyslipidemia.

	Dyslipidemic SLE Patients	Non-dyslipidemic SLE Patients	P Value
TNF α (pg/ml)	36.4 \pm 31.0	54.3 \pm 67.9	.895
Right CIMT (cm)	0.07 \pm 0.01	0.06 \pm 0.01	.559
Left CIMT (cm)	0.07 \pm 0.01	0.06 \pm 0.01	.097
Right PSV (cm/sec)	69.1 \pm 19.1	78.0 \pm 13.8	.160
Right EDV (cm/sec)	27.9 \pm 8.4	28.6 \pm 8.5	.850
Right RI	0.60 \pm 0.09	0.65 \pm 0.07	.091
Left PSV (cm/sec)	77.5 \pm 19.9	81.4 \pm 18.1	.593
Left EDV (cm/sec)	32.9 \pm 6.9	32.5 \pm 9.0	.904
Left RI	0.58 \pm 0.08	0.57 \pm 0.14	.884

Abbreviations: TNF α , tumor necrosis factor alpha; CIMT, carotid intima-media thickness; PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index.

Table 6. Results of TNF α Levels and Duplex Sonography Findings (mean \pm standard deviation) for Systemic Lupus Erythematosus (SLE) Patients With and Without Lupus Nephritis.

	SLE Patients With LN	SLE Patients Without LN	P Value
TNF α (pg/ml)	39.1 \pm 35.9	53.8 \pm 68.3	.880
Right CIMT (cm)	0.06 \pm 0.01	0.06 \pm 0.01	.961
Left CIMT (cm)	0.07 \pm 0.01	0.06 \pm 0.01	.027
Right PSV (cm/sec)	72.1 \pm 20.8	76.6 \pm 12.7	.524
Right EDV (cm/sec)	26.6 \pm 8.1	29.4 \pm 8.4	.377
Right RI	0.63 \pm 0.10	0.63 \pm 0.07	.969
Left PSV (cm/sec)	78.6 \pm 17.2	80.9 \pm 19.5	.748
Left EDV (cm/sec)	33.4 \pm 6.2	2.1 \pm 9.3	.685
Left RI	0.59 \pm 0.07	0.57 \pm 0.14	.758

Abbreviations: LN, lupus nephritis; TNF α , tumor necrosis factor alpha; CIMT, carotid intima-media thickness; PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistive index.

could contribute to the premature atherosclerosis known to be present in patients with SLE patients.^{5,7} The present study found a significant difference in total serum cholesterol levels and serum triglyceride levels between SLE patients and the control group. However, there was no significant difference between SLE patients and controls in their high-density lipoprotein cholesterol levels. Additionally, there was no significant difference in the mean carotid intima-media thickness between SLE patients with dyslipidemia and those without dyslipidemia. This finding raises the possibility of other significant underlying factors for atherosclerosis, with or without dyslipidemia, as evidenced by increased CIMT in patients as compared to controls.

There was a significant correlation in SLE patients between SLEDAI and a number of findings, including an increased CIMT. These results indicate that increased CIMT as a marker of atherosclerosis may be related to disease activity in SLE patients and the resulting complex serum biochemistry. A significant correlation was seen as well between SLEDAI and total cholesterol and

low-density lipoprotein cholesterol, in agreement with Ardoin et al.²¹ Their study on children and adolescent lupus showed that active disease is characterized by elevated triglycerides and decreased high-density lipoprotein cholesterol. The pathophysiology of dyslipidemia in SLE involves a complex combination of cytokines, auto-antibodies, disease activity, medications, diet, and physical activity level, as well as other possible factors. The clinical implications of these findings indicate that if lipoprotein levels are abnormal, first-line therapy should involve diet and exercise interventions, usually for a minimum of 6 months. For persistent dyslipidemia, several pharmacologic therapies are available such as hydroxychloroquine, which improves lipid profiles and should be considered for all patients with SLE.

Our study showed no significant correlation between SLEDAI and serum TNF α levels, in contrast to studies by Sabry et al who found significant correlations between TNF α and interleukin-6 serum levels and the SLEDAI score.^{6,8} This may be due to the low number of SLE patients with an SLEDAI of more than 10 in our study

(only 10 out of the 30 SLE patients), while in the studies by Sabry et al there were 20 patients (of a total of 40) with SLEDAI scores greater than 10.

Conclusion

The high levels of TNF α in SLE patients indicate the activation of an immune response. The increased common carotid artery intima-media thickness seen in lupus patients in this study was not correlated with TNF α levels and the presence or absence of dyslipidemia, denoting an underlying combining factor for early atherosclerosis in lupus patients other than those. Increased CIMT was seen in lupus nephritis patients, which may denote a role for inflammation in early atherosclerosis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

- Petri M: Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. *Lupus* 2000;9(3):170–175.
- Shoenfeld Y, Gerli R, Doria A, et al: Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005;112(21):3337–3347.
- Tedgui A, Mallat Z: Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol Rev* 2006;86(2):515–581.
- Vanden WB, Vermeulen L, De Wilde G, et al: Signal transduction by tumor necrosis factor and gene regulation of the inflammatory cytokine interleukin-6. *Biochem Pharmacol* 2000;60(8):1185–1195.
- Svenungsson E, Fei GZ, Jensen-Urstad K, et al: TNF- α : a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. *Lupus* 2003;12(6):454–461.
- Sabry A, Sheashaa H, El-Husseini A, et al: Proinflammatory cytokines (TNF-alpha and IL-6) in Egyptian patients with SLE: its correlation with disease activity. *Cytokine* 2006;35(3-4):148–153.
- Reichin M, Fesmire J, Quintero-Del-Rio, et al: Autoantibodies to lipoprotein lipase and dyslipidemia in systemic lupus erythematosus. *Arthritis Rheum* 2002;46(11):2957–2936.
- Sabry AA, Kalil AM, Abd El-Rahim M, et al: Proinflammatory cytokines (TNF alpha and IL-6) in Egyptian SLE patients with lupus nephritis: is it correlated with disease activity? *Eur J Gen Med* 2005;2(4):153–158.
- Hodis HN, Mack WJ, LaBree L, et al: Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med* 1996;124:548–556.
- O'Leary DH, Polak JF, Kronmal RA, et al: Thickening of the carotid wall: a marker for atherosclerosis in the elderly? *Stroke* 1996;27:224–231.
- O'Leary DH, Polak JF, Kronmal RA, et al: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;340:14–22.
- Pignoli P, Tremoli E, Poli A, et al: Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986;74:1399–1406.
- Greenland P, Alpert JS, Beller GA, et al: 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010;122:2748–2764.
- Nambi V, Chambless L, Folsom AR, et al: Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol* 2010;55:1600–1607.
- Caccipaglia F, Zardi EM, Coppolino G, et al: Stiffness parameters, intima-media thickness and early atherosclerosis in systemic lupus erythematosus patients. *Lupus* 2009;18(3):249–256.
- Serikova S, Kozlovskaia NL, Shilov EM: Lupus nephritis as a factor of atherosclerosis risk in patients with systemic lupus erythematosus. *Ter Arkh* 2008;80(6):52–58.
- Sazliyana S, Mohd Shahrir MS, Norella KCT: Implications of immunosuppressive agents in cardiovascular risks and carotid intima media thickness among lupus nephritis patients. *Lupus* 2011;20(12):1260–1266.
- Barth JD: Carotid intima media thickness and beyond. *Curr Drug Targets Cardiovasc Haematol Disord* 2004;4: 129–145.
- Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). *Arthritis Rheum* 1997;40:1725.
- Pfeffer K: Biological functions of tumor necrosis factor cytokines and their receptors. *Cytokine Growth Factor Rev* 2003;14(3-4):185–191.
- Ardoin SP, Sandborg C, Schanberg LE: Management of dyslipidemia in children and adolescents with systemic lupus erythematosus. *Lupus* 2007;16(8):618–625.