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ORIGINAL ARTICLE

Hyperhomocysteinemia and metabolic syndrome are risk factors for sub-clinical atherosclerosis in women with systemic lupus erythematosus

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KEYWORDS

Systemic lupus erythematosus;
Metabolic syndrome;
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Abstract *Aim of the work:* This study aimed to measure serum levels of homocysteine (sHcy) and to study the presence of the metabolic syndrome (MetS) in women with systemic lupus erythematosus (SLE) and to correlate them with disease activity, clinical status and sub-clinical atherosclerosis.

Patients and methods: This study included 30 adult SLE female patients and 20 age and sex matched apparently healthy volunteers as the control group. Disease activity and damage were assessed using the SLE disease activity index (SLEDAI) score and Systemic Lupus International Collaborative Clinics (SLICC) damage index, respectively. The MetS was diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII). Total sHcy was measured by enzyme immunoassay. B mode ultrasound was done to measure the carotid intima-media thickness (CIMT).

Results: The mean CIMT (0.97 ± 0.26 mm) and sHcy (46.96 ± 22.07 μmol/L) were significantly higher in patients compared to the controls (0.43 ± 0.22 mm and 4.19 ± 1.49 μmol/L, respectively) ($p < 0.001$). The mean CIMT significantly correlated ($p < 0.001$) with patient age ($r = 0.52$), disease duration ($r = 0.69$), SLEDAI ($r = 0.66$), SLICC ($r = 0.82$), sHcy ($r = 0.53$), total cholesterol ($r = 0.51$), triglycerides ($r = 0.77$), low density lipoprotein ($r = 0.53$), fasting blood sugar ($r = 0.75$), systolic ($r = 0.68$) and diastolic ($r = 0.64$) blood pressure and negatively with C3

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($r = -0.54$), high density lipoprotein (HDL) ($r = -0.56$), platelets ($r = -0.55$) and white blood cell counts ($r = -0.51$). Patients with MetS had statistically significantly higher CIMT (1.25 ± 0.09 mm) and sHcy (56 ± 19.31 μmol/L) versus those without (0.79 ± 0.16 mm and 40.5 ± 21.9 μmol/L, $p < 0.001$ and $p = 0.048$, respectively).

Conclusion: We can conclude that SLE itself is considered a risk factor for accelerated atherosclerosis and this is amplified by multiple factors.

1. Introduction

Women with systemic lupus erythematosus (SLE) have more than fivefold increase in the risk of coronary heart disease (CHD) events particularly related to premature atherosclerosis that rises to a 50-fold increase in younger patients [1]. Since the recognition of high cardiovascular disease (CVD) risk and its bimodal pattern of mortality, major advances in comprehensive understanding of the pathways of premature atherosclerosis have been started in SLE patients [2]. Recent advances stress on the interplay between lupus specific inflammatory factors including, inflammatory mediators, auto-antibodies, enhanced endothelial cell activation, corticosteroid-induced atherogenesis, and dyslipidemia associating renal disease together with traditional cardiac risk factors [3].

The metabolic syndrome (MetS); which is a lately defined clustering of CV risk factors characterized by obesity, arterial hypertension, hyperglycemia, insulin resistance, elevation of triglycerides and low high-density lipoprotein (HDL), has been shown during the last decade to be an independent CV mortality predictor [4], with a special concern in women who run a twofold risk to contract severe CVD [5]. MetS is closely related to the inflammatory response, it has been observed that proinflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) facilitate insulin resistance and that patients with MetS present high levels of C-reactive protein (CRP), IL-1β, interleukin-1 receptor antagonist (IL-1Ra), P-selectin, inter-cellular adhesion molecule-1 (ICAM-1) and leptin [6].

Homocysteine (Hcy), a thiol-containing amino acid which is produced during the metabolism of methionine, leads to insulin resistance through the inhibition of insulin-receptor kinase activity in vitro, also in an insulin resistant state, elevated Hcy plasma levels may be the result of hyperinsulinemia, as observed in animal models [7]. Therefore, Hcy may be a cause and/or a consequence of insulin resistance and is considered an indicator of risk for the development of atherogenesis [8].

It has become inevitable to detect atherosclerosis as early as possible, many physiologic measurements for plaque and endothelial dysfunction are now available, however measurement of the carotid artery intima-media thickness (CIMT), by a non invasive high-resolution B-mode ultrasound technique is now commonly accepted as a surrogate marker for subclinical atherosclerosis [9].

This study aimed to the measure serum levels of Hcy and to study the presence of the MetS in women with systemic lupus erythematosus and to correlate them with disease activity, clinical status and subclinical atherosclerosis.

2. Patients and methods

2.1. Participants

This study included 30 female patients who were regularly being followed up at the outpatient clinic and the inpatient unit of the Rheumatology and Rehabilitation department, Benha University Hospitals between November 2012 and March 2013 and met the updated American College of Rheumatology (ACR), revised criteria for the classification of SLE [10] and 20 age and sex matched apparently healthy volunteers as the control group. None of the patients were known to have any symptoms suggestive of a CVD.

All patients were subjected to full history taking, thorough clinical examination recording of the disease duration, duration and doses of current prednisolone and/or disease modifying anti-rheumatic drugs (DMARDs), disease activity evaluated by the SLE disease activity index (SLEDAI) [11] and the cumulative end organ damage in SLE assessed using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index [12]. The local ethics committee of our institution (Benha University, Faculty of Medicine) approved the study and all participants gave a written informed consent before being enrolled in this study.

2.2. Laboratory investigations

Blood specimens were collected after an overnight fasting analyzed for complete blood count (CBC), erythrocyte sedimentation rate (ESR) by Westergren's method [13] in mm/1st h,
C-Reactive protein (CRP) by Latex agglutination test, Fasting blood sugar (FBS) Level, lipid profile [Total cholesterol (TC), triglycerides (TG), high density lipid cholesterol (HDL-C) and low density lipid cholesterol (LDL-C)], blood urea, serum creatinine levels, complete urine analysis (for urinary casts, hematuria, pyuria and albuminuria), 24 h protein in urine, anti-nuclear antibodies (ANA) by the immunofluorescence antibody test, anti-double stranded DNA (ds-DNA) antibodies by indirect fluorescent antibody test, anti phospholipid antibodies were considered positive in the presence of lupus anti-coagulants or anticardiolipin (IgG or IgM) at $\geqslant$40 units/ml.

Measurements of serum homocysteine (sHcy): Protein rich meals give higher Hcy values and were avoided late in the day before sampling. Serum samples were allowed to clot for no more than 30 min before centrifugation and separation and kept on ice prior to separation. Total sHcy was then measured with the Axis® Homocysteine Enzyme Immunoassay (EIA)