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Original Article

Predicting flow-mediated dilation of brachial artery in systemic lupus erythematosus patients by reproducible and operator-independent inflammatory and immunologic markers and development of a novel score

Supratip Kundu [a], *Vishal Parmar* [b], *Sayantan Ray* [c,*], *Kaushik Basu* [d], *Manjari Saha* [e], *Anindya Mukherjee* [f], *Dibbendhu Khanra* [g], *Nikhil Sonthalia* [g], *Arunansu Talukdar* [g]

Departments of [a]Cardiology, [f]Community Medicine and [g]General Medicine, Medical College and Hospital, Kolkata, India; [b]Department of General Medicine, Katihar Medical College, Bihar, India; Departments of [c]Endocrinology and Metabolism, [d]Rheumatology and [e]General Medicine, IPGMER and SSKM Hospital, Kolkata, India

ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 21 July 2015
Available online 20 October 2015

Keywords:
Systemic lupus erythematosus
Inflammation
Endothelial dysfunction
Flow mediated dilation

ABSTRACT

Background: Early detection of endothelial dysfunction in patients with systemic lupus erythematosus (SLE) is important since they show accelerated atherosclerosis and an increased risk of cardiovascular mortality.

Aim: The aim of the study was to describe the correlation of flow-mediated dilation (FMD) with common inflammatory and immunological markers in patients with SLE. An attempt was made to predict a model of FMD with the help of these markers.

Material and methods: The study included 44 treatment-naive SLE patients as per American College of Rheumatology (ACR) criteria (1982) and 44 age- and sex-matched healthy controls. Each group consists of 42 females and 2 males. FMD of the brachial artery by B-mode ultrasonography was performed in both groups to compare the FMD value. Serum hsCRP, fibrinogen, uric acid, fasting insulin, serum ferritin, total cholesterol, triglyceride, VLDL, LDL, and HDL levels were measured as markers of inflammation in SLE patients to determine whether there was any correlation with FMD.

Results: There were no significant differences in age and gender between the SLE and control groups. The mean FMD was 16.85 ± 10.64 and 21.89 ± 4.6 among cases and controls, respectively. FMD was significantly less among SLE patients ($p = 0.005$). The hsCRP, uric acid, fibrinogen, insulin resistance, and ferritin values were found to have significant correlations with FMD values among treatment-naive SLE patients. Multiple linear regression by the ENTER method was used to predict a model of FMD: FMD = 48.252 − 1.565 hsCRP − 0.143 fibrinogen − 0.217 uric acid + 0.001 ferritin + 7.658 IR.

Conclusion: Inflammatory markers of SLE, such as hsCRP, fibrinogen, insulin resistance, and uric acid positively correlate with FMD values. FMD can be predicted from the value of these biochemical parameters.

* *Corresponding author.*
E-mail address: sayantan.ray30@gmail.com (S. Ray).

http://dx.doi.org/10.1016/j.injr.2015.07.008

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse clinical manifestations. According to a study by Urowitz et al., the disease shows a bimodal mortality pattern. In the early years, mortality is due to severe infection, but after 5 years, mortality is related to atherosclerosis and consequent cardiovascular disease.[1] SLE patients show accelerated atherosclerosis and an increased risk of cardiovascular mortality, but the traditional cardiovascular risk factors calculated by Framingham 10-year cardiovascular disease risk score cannot alone predict this risk.[1,2]. In these low-risk patients, flow-mediated dilation (FMD) provides an accurate measurement of cardiovascular risk.[3] Alternately, if we consider the pathophysiology of atherosclerosis, immune mechanisms play an important role, particularly when plaque ruptures and atherothrombosis occur.[4] SLE being an autoimmune disease can account for this accelerated atherosclerosis.[5] Although endothelial dysfunction is the earliest atherosclerotic change, and the FMD of the brachial artery is a sensitive tool to pick up the change, it is a cumbersome process with significant intra- and interindividual observer variations.[6] In the present study, we attempted to look for correlations between FMD and various inflammatory and immunological markers of SLE. The primary purpose of this study was to predict a model of FMD with the help of these markers, which are mostly automated, easily reproducible, and with almost negligible interindividual variation. This will aid in cardiovascular risk prediction for these patients without the need for FMD, which is a cumbersome and observer-dependent process.

2. Material and methods

From July 2011 to June 2012, a total of 44 consecutive patients, admitted with a diagnosis of SLE according to the American College of Rheumatology (ACR) 1982 criteria in Medical College and Hospital, Kolkata, were enrolled in this study. Patients with a previous history of smoking, alcohol abuse, myocardial infarction, angina pectoris, congestive heart failure, peripheral arterial disease, current pregnancy, delivery within 3 months, or malignancy were excluded from the study. Informed written consent was obtained from all patients. The study protocol was approved by the Institutional Ethics Committee. All 44 patients were treatment-naive, as treatment may alter the course of the disease and steroids may modify the lipid profile of these patients. Forty-four age- and sex-matched healthy controls were selected based on their history and a physical examination from the hospital staff. The age distributions among the study and control groups were similar. Each group consisted of 42 females and 2 males.

Endothelial function was assessed by means of flow-mediated vasodilatation of the brachial artery, using B-mode ultrasonography (AU 500) in both groups. All measurements of brachial artery diameter and FMD were performed after the diagnosis and before starting treatment. However, in these patients, symptoms were present for 0–48 months before diagnosis, more so in cases of autoimmune hemolytic anemia. FMD was performed in the morning, in a quiet and dark room, and at controlled ambient temperatures between 20 °C and 26 °C. The electrocardiogram (ECG) was continuously monitored. Female participants were examined during the follicular phase of their menstrual cycle. Studies were conducted after an overnight fast of at least 10 h (water was permitted), with the subjects supine and after 10 min of rest. The subjects' right arms were comfortably immobilized in an extended position, allowing for ultrasound scanning of the brachial artery 5–10 cm above the antecubital fossa. The brachial artery was scanned in longitudinal sections using an HDI 5000 Ultrasound Instrument (Philips Medical Systems, Bothell, WA) with a 5–12 MHz linear array transducer. One experienced sonographer collected all images. Images were digitalized from the video output of the ultrasound machine using a frame grabber under the control of custom software on a personal computer. Image acquisition was gated with an ECG signal so that images were captured at end diastole in each cardiac cycle. The diameter of the brachial artery was measured incident with the R wave of the electrocardiograph trace (Di). Then, ischemia was induced by inflating the pneumatic cuff to a pressure 50 mmHg above the systolic pressure in order to obliterate the brachial artery and induce ischemia. After 5 min, the cuff was deflated and the diameter was measured after 45 s postdeflation (Df). FMD was calculated according to the following formula:

$$\text{FMD} = \left[\frac{\text{Df} - \text{Di}}{\text{Di}}\right] \times 100$$

The means and standard deviations of the FMD values of both groups were determined. An unpaired *t*-test was performed to compare the value of FMD between both groups. A p value <0.05 was considered statistically significant.

Serum hsCRP, fibrinogen, uric acid, fasting insulin, serum ferritin, total cholesterol, triglyceride, VLDL, LDL, and HDL were measured in SLE patients. hsCRP was measured by the immunoturbidimetry method in an autoanalyzer (normal, 0.06). Fibrinogen levels were measured in a coagulometer CA 500 by the Clauss fibrinogen assay (normal value 150–300 mg/dl). Uric acid levels were measured by photometry (normal value 3.5–7.2). C3 levels were measured by nephelometry. Triglycerides were measured by the spectrophotometric method. HDL and LDL levels were measured by the polyethylene glycol precipitation method and oxidase method, respectively. Ferritin levels were measured by the spectrophotometric method. Serum fasting insulin levels were measured in fasting serum samples by monobind insulin microplate ELISA. Fasting blood sugar levels were estimated by the GOD/POD method. From these variables, a simple index of insulin resistance, i.e., Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), was calculated as

$$\frac{\text{I0} \times \text{G0}}{405}$$

where I0 is the fasting insulin level, G0 is the fasting glucose level, and 405 is a constant. FMD was taken as an independent parameter.