Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–7, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.02.009

● *Original Contribution*

ULTRASONOGRAPHIC EVALUATION OF RESISTIVE INDEX AND RENAL ARTERY STENOSIS IN PATIENTS WITH ANTI-PHOSPHOLIPID SYNDROME: TWO DISTINCT MECHANISMS?

Fabrizio Conti,* Fulvia Ceccarelli,* Antonietta Gigante,† Carlo Perricone,* Biagio Barbano,† Laura Massaro,* Francesca Romana Spinelli,* Cristiano Alessandri,* Guido Valesini,* and Rosario Cianci†

*Lupus Clinic, Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy; and †Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy

(*Received* 20 *October* 2014; *revised* 16 *February* 2015; *in final form* 19 *February* 2015)

Abstract—Renal involvement in anti-phospholipid syndrome (APS) is still relatively unknown and probably underestimated. The described lesions consist of renal artery stenosis (RAS), venous renal thrombosis and glomerular lesions. The resistive index (RI) of intra-renal arteries, expression of the degree of vascular resistance, has been analyzed in different nephropathies and observed to be associated with functional parameters and some histologic features. In contrast, there are no studies on patients with APS. We evaluated the presence of a pathologic RI and RAS in a cohort of patients with APS. The study protocol included ultrasonographic assessment to measure the RI (RIs >0.7 were considered pathologic) and to determine the presence of RAS. We enrolled 36 patients with APS, 13 with primary APS and 23 with the form associated with systemic lupus erythematosus (SLE, secondary APS). As controls, we enrolled 10 anti-phospholipid antibody carriers, 10 patients with SLE without renal involvement and 14 age- and sex-matched healthy patients. A pathologic RI was identified in five patients with APS (13.9%) and in none of the anti-phospholipid antibody carriers ($p = 0.00007$). Four of the five (80%) patients with a pathologic RI had secondary APS. Three patients, all with primary APS, had RAS. The almost exclusive association of a pathologic RI with secondary APS and of RAS with primary APS suggests the involvement of two pathogenic pathways in the development of these different manifestations. The hypercoagulability status driven by APS could play a central role in the determination of RAS in patients with primary APS, whereas the activation of mTORC (mammalian target of rapamycin complex) pathways could be the pathogenic mechanism inducing development of a pathologic RI. (E-mail: fabrizio.conti@uniroma1.it) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Resistive index, Renal artery stenosis, Anti-phospholipid syndrome.**

INTRODUCTION

Anti-phospholipid syndrome (APS) is characterized by the occurrence of arterial and/or venous thrombosis, recurrent abortions or fetal loss and circulating anti-phospholipid antibodies (aPLs). The kidney appears to be a target organ in patients with APS, in both primary APS (PAPS) and in the form associated with systemic lupus erythematosus (SLE) (secondary APS [SAPS]) (Uthman and Khamashta 2006). The renal involvement can occur as renal artery stenosis (RAS), venous thrombosis, thrombotic micro-angiopathy (TMA) and other histologic features, called APS nephropathy (Gigante et al. 2009; Uthman and Khamashta 2006). RAS is a frequent feature of patients with APS and is associated with important clinical manifestations, such as hypertension (Sangle et al. 2003).

The renal resistive index (RI) is an index of intra-renal arterial resistance, proposed in the differential diagnosis of several nephropathies (Krumme 2006; Parolini et al. 2009; Rosato et al. 2012). An increase in RI values has been observed in pathologic conditions such as renal transplant acute rejection, renal vein thrombosis, acute tubular necrosis, hemolytic uremic syndrome and crescent and proliferative glomerulonephritis (Naesens et al. 2013; Quaia and Bertolotto 2002). Some data suggest a correlation with

Address correspondence to: Fabrizio Conti, Lupus Clinic, Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Viale del Policlinico 155, 00161, Rome, Italy. E-mail: fabrizio.conti@uniroma1.it

impairment of renal function and association with some histologic features (Chen et al. 2014; Conti et al. 2014a; Ikee et al. 2005; Naesens et al. 2013; Quaia and Bertolotto 2002; Mostbeck et al. 1991; Platt et al. 1990, 1997; Sugiura and Wada 2009, 2011; Sugiura et al. 2004). To the best of our knowledge, no studies have evaluated the prevalence of RI modifications in patients affected by APS so far.

Our aim, therefore, was to determine the presence of modification of this RI, evaluated by Doppler ultrasound (US), in this specific group of patients. Moreover, we evaluated the presence of RAS, and finally, we evaluated any association between the presence of a pathologic renal artery RI and autoantibodies and cardiovascular risk factors.

METHODS

In this cross-sectional study, we enrolled 36 patients affected by APS attending the Lupus Clinic of Sapienza University of Rome: 13 patients with PAPS and 23 with SAPS. APS was classified according to the international consensus statement of classification criteria (Miyakis et al. 2006). The diagnosis of SLE was made according to the 1997 American College of Rheumatology revised classification criteria (Hochberg 1997).

As controls, we enrolled 10 aPL carriers, 10 patients with SLE without renal involvement and 14 age- and sex-matched healthy patients. We excluded all patients with acute and chronic kidney diseases, known renal artery stenosis, heart failure, hepatic disease and urinary tract obstruction.

We collected clinical and laboratory data on a standardized, computerized, electronically completed form, which included demographic characteristics, past medical history, comorbidities, and previous and concomitant treatments. The study protocol included a complete physical examination, blood tests and ultrasonographic assessment. The study was conducted in accordance with the protocol, good clinical practice principles and the Declaration of Helsinki. The local ethics committee approved the study, and all patients signed an informed consent.

Clinical and laboratory evaluation

Clinical manifestations included venous and/or arterial thrombosis and pregnancy morbidity as stated in the APS classification criteria (Miyakis et al. 2006). Vascular thrombosis has been defined as one or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ, confirmed by objective validated criteria (*i.e.,* unequivocal findings of appropriate imaging studies or histopathology) (Miyakis et al. 2006). Pregnancy morbidity is defined as (i) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th wk of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or (ii) one or more premature births of a morphologically normal neonate before the 34th wk of gestation because of eclampsia or severe pre-eclampsia defined according to standard definitions; recognized features of placental insufficiency; or three or more unexplained consecutive spontaneous abortions before the 10th wk of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded (Miyakis et al. 2006).

We evaluated the presence of risk factors potentially influencing the RI and RAS: specifically, we registered the presence of concomitant hypertension, diabetes, dyslipidemia and smoking.

Each subject underwent peripheral blood sample collection. The serum sample was stored at −20°C until assayed. With respect to auto-antibodies, anti-cardiolipin (aCL) (IgG and IgM isotype) and anti-β_2-glycoprotein I (anti-β_2-GPI) (IgG and IgM isotype) were assessed by ELISA (Diamedix, Miami, FL, USA), and lupus anticoagulant (LA) was assessed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies) (Pengo et al. 2009). In patients with APS associated with SLE, we evaluated anti-nuclear antibodies (ANAs) by indirect immunofluorescence assay on HEp-2, anti-dsDNA by indirect immunofluorescence on *Crithidia luciliae* in accordance with the manufacturer's instructions (Orgentec Diagnostika, Mainz, Germany), and ENA (anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP) by ELISA (Diamedix). Finally, we determined C3 and C4 serum levels (mg/dL) by nephelometry. We also evaluated renal involvement by assessing serum creatinine, blood urea nitrogen and estimated glomerular filtration rate using the CKD-EPI equation (Levey et al. 2009).

Renal Doppler ultrasound

Kidney Doppler US (Aplio Ultrasound System SSA-790 with a convex 3.5-MHz probe, Toshiba, Tokyo, Japan) was performed by a single expert investigator (R.C.) who was blinded to the clinical features of patients. Renal Doppler evaluation was performed in the arcuate arteries in the region of the corticomedullary junction and the interlobar arteries along the border of medullary pyramids by placing the probe at three different positions (mesorenal, superior and inferior pole) over both kidneys, under the guidance of color flow mapping. The gain was set so that background echoes were barely visible. The Doppler gate width was kept small, and the angle of insonation was corrected (Platt et al. 1997). An anterior approach was used to detect the origin of the renal artery,