VOLUME-7, ISSUE-4, APRIL-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Clinical Research

NON-INVASIVE MEASUREMENT OF ENDOTHELIAL DYSFUNCTION IN EARLY RHEUMATOID ARTHRITIS AND ITS CORRELATION WITH BIOCHEMICAL MARKERS OF DYSLIPIDEMIA AND CHRONIC INFLAMMATION.

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Thesis topic:

Non-invasive measurement of endothelial dysfunction in early rheumatoid arthritis and its correlation with biochemical markers of dyslipidemia and chronic inflammation.

Summary of the proposal: Cardiovascular disease is the most common cause of mortality in rheumatoid arthritis patients. The high prevalence of cardiovascular disease in this population is attributable to accelerated atherosclerosis which often occurs in absence of traditional risk factors. Accelerated atherosclerosis in rheumatoid patients occurs as a consequence of chronic inflammation, the chronic inflammatory mediators predispose these patients to endothelial dysfunction resulting in accelerated atherosclerosis

Normal endothelium maintains vascular tone by releasing a number of vasoactive substances, the most important of which is nitric oxide(NO). Normal endothelium releases NO in response to shear stress which in turn causes relaxation of vascular smooth muscles and consequent dilatation of the vessel. Endothelial dysfunction is defined as an impaired ability of any artery to dilate in response to physical or chemical stimuli due to decreased release or increased breakdown of NO.

Brachial artery flow mediated vasodilatation(FMD) is a non-invasive physiological measure of endothelial dysfunction evaluated by high resolution ultrasonography(USG) of brachial artery. First described in 1992 by Celermajer et al, FMD evaluates the endothelial function on the basis of production of NO by endothelium after an artificially induced ischaemia(by pneumatic compression of forearm with sphygmomanometer cuff with pressure level raised to suprasystolic values). This ischemia causes distal peripheral resistance to fall and reactive hyperaemia leading to increased flow through the artery following cuff deflation. This increased flow will lead to shear stress mediated NO release from normal endothelium and hence dilatation of the artery. The FMD value is calculated as the difference between maximum post-occlusion diameter(D2) and the baseline diameter(D1) and is expressed as a percentage(FMD%).
FMD%=(D2-D1)x100D1

Carotid intima-medial thickness(IMT), determined by high resolution B-mode USG, is the useful non-invasive structural measure of sub-clinical cardiovascular disease. It constitutes an excellent surrogate marker of atherosclerotic vascular disease. Increases carotid IMT and increased frequency of carotid plaques have been described in rheumatoid arthritis patients with or without classic cardiovascular risk factors compared with ethnically matched controls. There are also evidences of association of carotid IMT with inflammatory markers.

Early rheumatoid arthritis is defined as RA of less than 2yrs duration and detection of early endothelial dysfunction in these patients by FMD will lead to more chance of reversibility by DMARD therapy. There are paucity of studies in India in regards to non-invasive evaluation of endothelial dysfunction in rheumatoid arthritis population and its correlation with markers of chronic inflammation and dyslipidemia both before and after therapy- in these background the study is undertaken.

Aims and objectives:

Endothelial dysfunction is the primordial cause of all vascular complications of rheumatoid arthritis. Albeit it is very difficult to measure endothelial dysfunction directly, it can be quantified indirectly by non-invasive measurement viz. FMD of brachial artery by high resolution USG. The carotid IMT measurement also predicts the risk of early atherosclerosis in this sub-group of patients but there are generally conflicting data in this regard.

The high resolution USG is a widely available, cost-effective tool to measure FMD and IMT. The procedure is also well tolerated by the patients and because of almost no adverse effect of USG multiple follow-ups can be done .

This study aims to determine the role of FMD & IMT in prediction of atherosclerotic cardiovascular disease risk in rheumatoid arthritis patients and to correlate those data with chronic inflammatory markers viz c-reactive protein(CRP) and dyslipidemia markers viz LDL-C, HDL-C and total cholesterol levels both before and after therapy.

Specific objectives of the study:

1. To study the prevalence of endothelial dysfunction non-invasively by flow mediated vasodilatation of brachial artery by high resolution USG in early rheumatoid arthritis patients.
2. To study the carotid intima-medial thickness by M-mode USG in this patient population to see the prevalence of atherosclerosis.
3. To correlate chronic inflammatory markers CRP levels and dyslipidemia markers LDL-C, HDL-C and total cholesterol levels with FMD and carotid IMT both before and after treatment with DMARDs(methotrexate, sulfasalazine and hydroxychloroquine).

Material and methods:

Study area: Department of Radiodiagnosis, IPGMER Kol-20. and Rheumatology Centre, IPGMER Kol-20.

Study population:

Inclusion criteria:

a. Diagnosis of rheumatoid arthritis based on American College of Rheumatology criteria(revised 1987).
b. Disease duration less than 2yrs from onset.

Exclusion criteria:

a. Age more than 60 yrs or less than 18 yrs at entry.
b. Co-morbid diseases: diabetes, obesity(BMI>30), familial dyslipidemia, coronary artery disease, cerebro-vascular accident, peripheral vascular disease, hypothyroidism, renal disease(serum cr>3mg/dl or cr clearance <30ml/24hrs, liver disease, Cushings syndrome

c. Current or recent(within past 3 months) pregnancy.
d. Concurrent treatment with lipid lowering drugs, beta blockers, OCPs, estrogen, progestines, thyroxin, vitamin E, steroids(other than prescribed under trial supervision)

Study period: From Jan 2010 to July 2011

Sample size: Total number of patient should comprise at least 30.

Sample design: Cases are the consecutive patients(from study date) suffering from rheumatoid arthritis, who are fulfilling all the criteria of study population and are willing to participate in the study will be included.

Study technique:
Flow mediated vasodilatation of brachial artery:
The procedure will be performed by a single radiologist. The subjects will be required to abstain from alcohol, caffeine and smoking at least 8 hours prior to the procedure. The subject will lie supine at least for 10 minutes.

The right brachial artery will be scanned in longitudinal section 2-15 cms above the elbow with B-mode USG images using 5-10 MHz linear array transducer. The centre of the artery will be identified where clearest picture of anterior and posterior intimal layers are available. In this suitable transducer position which is to be kept constant throughout the procedure. A resting scan will be obtained- the luminal diameter and the velocity profile of arterial flow will be measured by pulsed Doppler.

A sphygmomanometer cuff placed around forearm distal to the scanned region will be inflated to 200mm of Hg for 4.5 minutes and then released. This will induce increased flow. A second scan will be taken at this stage and luminal diameter and flow measured. Endothelial dysfunction will be considered to be present when FMD is below 4.5%.

Carotid ultrasonography:
The procedure will be performed and interpreted by a single radiologist. Both carotid arteries are scanned with the subject in supine position with slight hyperextension of the neck in multiple planes to identify atherosclerosis(plaque protruding into arterial lumen >50%). Intimamedial thickness will be measured from end diastolic M-mode images of the far wall of the distal common carotid artery in a location not containing the plaque. Mean value of two sides(right and left) will be taken.
Accuracy and reproducibility of both the above measurements have been established.

Lipid profile:- Total cholesterol, LDL-C, HDL-C as marker of dyslipidemia and hs-CRP will be measured as chronic inflammatory markers at regular intervals.

Each of the measurements (viz FMD, carotid IMT, hs-CRP lipid profiles) will be evaluated at baseline and after institution of drug therapy(viz methroxate 7.5mg per week, sulfasalazine 2gms per day, Hydroxychroloquine 400mg/day). Minimum one follow up will be done at 6 months from the onset of drug therapy.

Parameters to be studied:
1. Intimamedial thickness of both common carotid arteries. Mean values of the measurements will be taken.
2. Flow mediated vasodilatation of right brachial artery.
3. Correlation of carotid IMT and flow mediated vasodilatation with hs-CRP level and LDL-C, HDL-C and total cholesterol level at baseline and at 6 months and 1 year of drug therapy.

Study tools:
1.Ultrasound machine of Siemens, make Acuson with linear array broadband transducer (5-10 MHz) with selectable frequency.
2.ercury sphygmomanometer.

Study design: Prospective study.

Plan for analysis of data: Obtained data regarding carotid IMT, brachial FMD, serum LDL-C, HDL-C, and hs-CRP level will be compared with existing data using standard statistical techniques.

Funding for study: No financial support or grant is necessary for the study as the USG machine belongs to Govt. of West Bengal.

Review of literatures:
When blood flow increases through a blood vessel, the vessel dilates. This phenomenon- flow dependant dilatation has been demonstrated in a number of vessels in vivo and in vitro in both animals and humans(1). Celermajer et al in 1992 first showed the utility of Doppler USG in diagnosis of endothelial dysfunction in a non-invasive way(2). Although at first FMD was used extensively to predict the presence or future development of atherosclerosis, now this measurement has a role in diagnosis of endothelial dysfunction in rheumatoid arthritis and other inflammatory arthritides(3). The method of measurement of brachial artery FMD is widely available cost effective, accurate, reproducible, without any side effects and is generally well accepted by the patients(4) but the procedure is technically demanding and has a long learning curve(5).

Carotid IMT is a good indicator of generalized atherosclerosis and coronary arterial disease(6). It provides early information of atherosclerosis in subclinical stages of disease in individuals at risk(7). Increased carotid and increased frequency of carotid plaques have been described in rheumatoid arthritis patients without classical cardiovascular risk factors(8).

Some studies have been done correlating chronic inflammatory marker CRP and FMD. An investigation evaluating 7 cardiovascular risk markers in 4113 subjects has demonstrated inverse relation between FMD and CRP (higher the CRP the lower the NO production and lower the FMD)-(9). In contrast one Brazilian study(10) did not find any significant correlation between CRP level and FMD.

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