DOI: 10.7860/JCDR/2016/20872.8751

Original Article

Internal Medicine Section

Flow Mediated Dilatation, Carotid Intima Media Thickness, Ankle Brachial Pressure Index and Pulse Pressure in Young Male Post Myocardial Infarction Patients in India

NIKHIL GUPTA[1], SUBHASH GIRI[2], VINITA RATHI[3], GAJENDER SINGH RANGA[4]

ABSTRACT

Introduction: Due to increase in Coronary Artery Disease (CAD) at a younger age, we should try to diagnose atherosclerotic process and population at risk, at the earliest. Flow Mediated Dilatation (FMD), Carotid Intima-Media Thickness (CIMT) and Ankle-Brachial Pressure Index (ABI) are probable markers for early atherosclerosis and may be useful in coronary risk stratification.

Aim: To compare and correlate the FMD, CIMT, ABI and Pulse Pressure (PP) in young male patients of Myocardial Infarction (MI) with age and sex matched healthy controls.

Materials and Methods: Eighty male patients of MI aged ≤45 years, who presented to the Cardiac Care Unit and Department of Medicine of Guru Teg Bahadur Hospital, Delhi, India, from November 2010 to April 2012 were recruited consecutively for this case control study and same number of age and sex matched healthy controls were also analyzed. Six weeks after MI, FMD of the brachial artery, intima media thickness of carotid artery, ABPI and PP were measured in the cases and compared with healthy controls.

Results: The FMD was lower among young patients of MI than controls (p<0.001). CIMT was higher among cases than controls (p=0.001). ABI was lower among cases than controls (p<0.001). Compared to controls, PP was higher among cases (p=0.001). In all subjects, a negative correlation between FMD and CIMT (r=–0.220, p=0.005) and a positive correlation between FMD and ABPI (r=0.304, p<0.001) was found. A statistically significant negative correlation was found between endothelial dependent FMD and PP among cases and control groups (r=–0.209, p=0.007).

Conclusion: Biophysical parameters were deranged in young post MI patients. Majority of our young male patients fell in low risk Framingham risk score but still they manifested with CAD. Despite six weeks of treatment among young male patients of MI, various biophysical parameters were still deranged.

Keywords: Biophysical parameters, Coronary artery disease, Controls endothelial dysfunction, Glyceryl trinitrate, Young myocardial infarction

INTRODUCTION

Coronary Artery Disease (CAD) is a major threat worldwide. Indians are at a 3 to 4 fold greater risk for development of CAD than the rest of the world population [1-3]. In the Indian subcontinent there is a rising trend of CAD among younger people (age ≤45 yrs). In view of increasing CAD at a younger age, we should try to diagnose atherosclerotic process and population at risk, at the earliest. Various biophysical methods include - Flow Mediated Dilatation (FMD) for assessment of endothelial function, Carotid Intima Media Thickness (CIMT) which is considered as a surrogate marker of atherosclerosis and Ankle Brachial Pressure Index (ABI) to diagnose Peripheral Vascular Disease (PVD).

Brachial artery reactivity is a non-invasive ultrasonographic assessment of FMD. It is used to measure endothelium-dependent response to shear stress [4]. Studies have shown that FMD is a marker for increased cardiovascular risk. It has been observed that FMD correlates with impaired endothelium-dependent relaxation in the coronary arteries [5]. CIMT is a non-invasive tool that can be used for cardiovascular risk stratification in individuals [6].

ABI is a useful tool for prediction of overt atherosclerosis and marker of cardiovascular risk (<0.9. ABI is strongly associated with cardiovascular diseases. Previous studies have found that those with lower extremity arterial disease are 1.5 to 2 times more likely to experience a clinical cardiovascular event [7]. As shown in studies, ABI has an inverse association with mortality [8]. Many prospective studies have shown that a low ABI (<0.9) can predict CVD. ABI, particularly in elderly men with morbidities as hypertension and type II diabetes can be used to predict mortality [9].

Pulse Pressure (PP) is an index of morphologic deterioration reflecting arterial thickening, fibrosis and calcification of blood vessels. Amongst PP, systolic or diastolic blood pressure, PP was found to be a better predictor of cardiovascular events [10].

Various studies have been done on biophysical parameters among the MI patients. However, there is scarce data on biophysical parameters among the young patients of MI in India.

The objectives of this study were:

Primary: To compare the FMD, CIMT, ABI and PP in young male patients of Myocardial Infarction (MI) with age and sex matched healthy controls.

Secondary: To correlate FMD with CIMT, ABI and PP among cases and controls.

MATERIALS AND METHODS

We consecutively recruited the patients of MI aged ≤ 45 yrs [11] who presented to the Cardiac Care Unit and Department of Medicine of Guru Teg Bahadur Hospital, Delhi, India, from November 2010 to April 2012. The study was a case control study. Those who qualified the criteria of inclusion and exclusion and gave consent for the study were enrolled. The post MI survivors were followed up in preventive cardiac clinic and OPDs of medicine. After six weeks or more of MI - FMD, CIMT and ABI were measured. The

controls were age and sex matched volunteers from hospital staff and unrelated attendants of patient.

Healthy controls were recruited based on history, examination including blood pressure and investigations including lipid profile, blood sugar, HbA1c and ECG, only healthy controls were recruited. Controls with any risk factor for CAD were excluded. All ultrasound measurements were performed in the morning by a single immensely experienced radiologist. Cases were on their regular therapy (ecospirin, ramipril, atorvastatin, propranolol, clopidogrel) and had taken their usual dose of morning medicine. The smokers abstained from smoking. Finally the data of 80 male patients of MI and same number of age and sex matched healthy controls were analysed. The study was approved by Institution Review Board and ethical clearance was obtained. The informed consent was taken from the patients. The diagnosis of MI was made by - Revised Definition of MI [12].

Criteria for Acute, Evolving, or Recent MI

Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI:

Typical rise of biochemical markers of myocardial necrosis with at least one of the following:

1. Ischemic symptoms.
2. Development of pathological Q waves in the ECG.
3. ECG changes indicative of ischemia (ST segment elevation or depression).
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Patients fulfilling these criteria were labelled as Cases (Group 1).

Exclusion Criteria

1. Patients with family history of premature (≤ 55 yrs) CAD.
2. Patient with liver disease [serum aminotransferase >3 fold of normal (>120 IU/l)] or renal disease (serum creatinine levels >1.5 mg/dl).
3. Patients with congestive heart failure, bronchial asthma and chronic allergic condition on medication, Buerger's disease, collagen vascular disease and Raynaud's disease.
4. Patients with chronic diseases such chronic renal failure, chronic liver disease, acute and chronic infectious diseases, malignancy dementia or other psychiatric illness.
5. Patients with impaired fasting glucose.

Flow Mediated Dilatation [13]

FMD was measured as below:

Subject preparation prior to ultrasonography includes:

1. Twelve hours fasting.
2. No caffeine/alcohol/ smoking within 24 hr/high fat diet/vitamin C prior to the study.

All subjects underwent ultrasonographic brachial artery diameter measurement as follows:

- First baseline was taken after 10 minute period of rest to allow acclimatisation.
- Endothelium dependent dilatation was assessed after the response to reactive hyperemia, induced by sudden deflation of pneumatic cuff placed on the ipsilateral arm and inflated to a pressure of 50 mmHg above systolic BP for five minutes. This technique releases nitric oxide from endothelium, leading to vasodilatation of artery that can be measured as an index of vasomotor function [13]. Second base line was assessed after further 10 minutes rest period to allow vessel recovery. Endothelium independent dilatation was assessed five minutes after sublingual administration of 0.5mg of Glyceryl trinitrate (GTN).

Carotid Intima Media Thickness

CIMT was performed as below:

CIMT was measured on both sides 1.5cm proximal to the carotid bifurcation in Common Carotid Artery (CCA) bilaterally in a plaque-free region by gray scale longitudinal image of the artery obtained with the help of 7.5 MHz -10MHz transducer on HDI 5000 or HDI 1500 ultrasound (Philips). Presence of any plaque, ulceration or calcification was also noted.

Ankle Brachial Pressure Index

The systolic blood pressure in both arms was taken with the blood pressure cuff and doppler probe, after a minimum of 10 min rest, greater of the two was taken as systolic BP of upper limb. If the difference between both the arms was greater than 10mmHg, the candidate was excluded. Systolic blood pressure in the Posterior Tibial (PT) or Dorsalis Pedis (DP) artery in the leg was taken. The higher of the two reading was taken as systolic BP at ankle. In case either the PT or DP ankle pulse was absent, the measurable reading was used to calculate the ABI.

The ABI was measured by dividing the systolic BP values obtained for leg by that of the brachial artery.

ABI

Normal value 1.0-1.1

Abnormal value < 1

Value <0.9 was highly significant for increased cardiovascular risk [14].

Pulse Pressure (PP)

Systolic and diastolic blood pressures were measured with an aneroid sphygnomanometer after a minimum of 10 min rest in the sitting position. PP was calculated as systolic minus diastolic blood pressure.

STATISTICAL ANALYSIS

Data is expressed as mean ± S.D. Unpaired student t-test was used to compare cases and control group. Correlation between FMD, CIMT, ABI and PP was done by correlation coefficient analysis. A p-value of <0.05 was taken as statistically significant.

RESULTS

[Table/Fig-1] shows clinical characteristics, mean data and laboratory values at the time of diagnosis of CAD among controls and cases. [Table/Fig-2] shows the number of controls and cases with various risk factors in our study. [Table/Fig-3] shows mean value ± S.D. of FMD, CIMT, ABI and PP among controls and cases respectively.

Framingham Risk Score

The number of cases with Framingham risk score < 10% (Low risk) were 63 (79.95%), 10%-20% (Intermediate risk) were 13 (16.46%) and score > 20% (High risk) were 3 (3.80%).

[Table/Fig-4] shows correlation between FMD, CIMT, ABI and PP among all the subjects (n=160).

[Table/Fig-5] shows the correlation between various risk factors of CAD and various biophysical parameters among cases.

A multivariate regression analysis was done between various risk factors and FMD, CIMT and ABI among cases. However, none of the risk factor correlated with these biophysical parameters significantly. Thus, these risk factors in our cases did not contribute significantly to FMD, CIMT and ABI and thus to the atherosclerotic process. Thus, taking controls with no risk factors did not create a bias to the values of FMD, CIMT and ABI.

Parameters	Group 0 (Control s) n = 80	Group 1 (Cases) N = 80	p-value
Age (yrs)	39.30±4.54	40.06±4.65	0.295 (n.s.)
BMI (kg/m^2)	22.51±0.45	24.43±1.63	<0.001
Waist circumference (cm)	87.15±1.31	90.99±3.62	<0.001
Systolic blood pressure (mmHg)	113.15±9.45	120.39±18.67	0.002
Diastolic blood pressure (mmHg)	76.16±13.73	76.23±11.29	0.975 (n.s.)
Blood sugar – fasting (mg/dl)	90.71±6.39	104.39±32.81	<0.001
Boold sugar – postprandial (mg/dl)	119.78±5.80	143.74±54.48	<0.001
LDL±SD (mg/dl)	78.90±11.57	98.64±32.91	<0.001
HDL–C±SD (mg/dl)	45.76±4.66	34.73±6.99	<0.001
TG±SD (mg/dl)	135.75±11.03	152.36±5.47	<0.001
Total cholesterol±SD (mg/dl)	145.84±19.02	161.06±36.81	0.001

[Table/Fig–1]: Clinical characteristics, mean data and laboratory values at the time of diagnosis of CAD among controls and cases.
p–value significant at < 0.05, n.s.– non significant–

Variable		Cases (n=80)
Smokers		69 (86.2%)
Known diabetics		8 (10%)
Newly detected diabetics		11 (13.75%)
Total diabetics		19 (23.75%)
Known hypertensives		12 (15%)
Newly detected hypertensive		5 (6.25%)
Total hypertensives		17 (21.25%)
BMI (kg/sqm)	23–24.99	38 (47.5%)
	≥25	25 (31.25%)
Central Obesity [Waist circumference (≥90 cm)]		46 (57.5%)

[Table/Fig–2]: Number of controls and cases with various risk factors.

Variable	Group 0	Group 1	p-value
FMD after inflation of cuff (%)	24.39 ± 5.55	12.89 ± 5.93	<0.001
FMD after GTN (%)	27.75 ± 4.94	19.44 ± 15.45	<0.001
CIMT of Rt. CCA (cm)	0.059 ± 0.009	0.066 ± 0.009	<0.001
CIMT of Lt. CCA (cm)	0.060 ± 0.007	0.066 ± 0.011	0.001
Average CMIT of both CCA (cm)	0.059 ± 0.007	0.066 ± 0.010	0.001
ABI	1.08 ± 0.048	1.04 ± 0.056	<0.001
PP (mm Hg)	36.99 ± 14.40	44.16 ± 11.24	0.001

[Table/Fig–3]: The mean value ± S.D. of FMD, CIMT, ABI and PP among controls and cases.
Group 0– controls, Group 1– cases, p–value significant at <0.05.

Variable	Average CIMT r value (p-value)	ABI r value (p-value)	PP R value (p-value)
Flow mediated dialatation after inflation of cuff	–0.220 (0.005)	0.304 (<0.001)	–0.209 (0.007)
Flow mediated dialation after GTN	–0.112 (0.159)	0.197 (0.012)*	–0.214 (0.059)
Pulse pressure (PP)	0.122 (0.126)	–0.177 (0.025)*	1
ABI	–0.185 (0.019)	1	–0.177 (0.025)*

[Table/Fig–4]: Correlation between FMD, CIMT, ABI and PP among all the subjects (n=160). p significant at <0.05, *p significant at <0.01.

DISCUSSION

The study was undertaken to assess the biophysical parameters in post MI young male patients at six weeks of follow-up. We assessed and compared the biophysical parameters i.e., FMD of brachial artery, CIMT and ABPI in young male post MI patients and age-sex matched healthy controls. Controls were taken as healthy i.e., without any risk factor. We also assessed various risk factors associated with young CAD.

Variable	Flow mediated dilatation after inflation of cnff	Flowmediated dilatation after GTN	Average CDJT	ABI
BMI	–0.164	–0.208	0.021	–0.072
WC	–0.111	–0.199	0.007	–0.009
SBP	–0.904	–0.058	0.010	–0.185
DBP	0.127	0.163	–0.038	–0.198
BS-F	0.084	–0.036	0.057	0.042
BS-PP	0.055	–0.075	0.028	0.101
TC	–0.005	–0.061	0.001	–0.206
HDL	0010	–0.110	–0.194	–0.043
LDL	0.011	0.094	–0.088	–0.198
Age of onset	0.001	0.041	0.146	–0.215
Smoking	–0.193	–0.131	0.009	–0.042

[Table/Fig–5]: Correlation between various risk factors of CAD and various biophysical parameters among cases.
None of the correlation was significant i.e., p–value was >0.05.

Biophysical parameters were assessed at six weeks to determine the usefulness of these parameters in follow-up of patients of MI. Since these parameters remain deranged post MI, they may be used for patient follow-up and aggressive treatment of CAD. Six weeks was taken as an arbitrary period so that these parameters may be assessed as early as possible and may be an indicator for an aggressive management.

We took patients below the age of 45years as there have been previous studies in India as Narsingan SN who defined young CAD as CAD occurring in patients less than 45years of age in Indian population [15]. CAD among young population is on the rise. Various Indian studies report that the patients suffering from acute MI below 45years to be 25%-40% [16].

It was observed that various risk factors as smoking, hypertension, diabetes, dyslipidemia and central obesity were significantly associated with premature CAD in male patients. In our study, the percentage of smokers in young CAD was observed to be 86.2%.

Increased CIMT is conventionally considered to be a marker of subclinical atherosclerosis. In our study, we observed that mean CIMT was significantly higher among cases as compared to controls. In our study, 12 (15%) cases had average CIMT value ≥ 0.08 cm, which is taken to be significant for cardiovascular risk [17,18]. Plaque was seen at Common Carotid Artery (CCA) A bifurcation among 2 (2.5%) cases. Presence of plaque is an independent risk factor for cerebro-vascular and cardiovascular accident. The low average CIMT (0.066 ± 0.010 cm) in our patients could be explained due to differences in ethnicity, young subjects and inter-observer variations. Also, our patients were on regular therapy for MI for six weeks.

FMD correlates with impaired endothelium-dependent relaxation in the coronary arteries [5]. In our study, we observed the mean value of endothelium dependent dilatation i.e., FMD after inflation of cuff among cases was significantly lower than the control group. These results were comparable to previous study as reported by Otikunta A. Naidu et al., who demonstrated significantly decreased flow mediated dilatation in patients when compared to control (9.42 ± 7.20% vs. 21.11 ± 9.16% p<0.01) [19]. FMD improves in response to drugs that have proven benefit on cardiovascular outcomes such as statins, anti-hypertensive drugs (including ACE-Inhibitors, angiotensin I receptor blockers, and calcium channel blockers) [20,21]. Despite the fact that our patients were on most of the above mentioned drugs for six weeks, the endothelial dependent dilatation was still significantly lower among cases than controls.

Various studies have shown the role of ABI in predicting cardio-vascular risk. In our study, mean value of ABI was significantly lower amongst the cases as compared with controls. Previous

studies have found that those with lower extremity arterial disease are 1.5 to 2 times more likely to experience a clinical CVD event [14]. Our results were in concordance with previously done studies by Erzen et al., and Gopal Premlatha et al., [10,22].

PP has been shown to be a risk factor for cardiovascular disease in many studies. High PP signifies an increased atherosclerotic process among the vessels. In our study, we found a statistically significant higher PP among cases as compared to controls. PP was found to be a better predictor of cardiovascular events than either systolic or diastolic blood pressure in the Framingham Heart Study [23].

As large artery stiffness increases, SBP rises and DBP falls, with a resulting increase in PP [24]. DBP falls with central artery stiffness and thus, may negative association with CAD [25].

Both PP and SBP components rise with increase in vascular resistance and large artery stiffness and hence, are correlated to each other. It was seen that increments in PP at a fixed SBP was associated with a greater risk for CHD than was increment in SBP at a fixed PP [23].

Majority of our young male patients fell in low risk Framingham risk score. Despite this finding, our young male patients with various risk factors suffered MI. This may be due to the fact that Framingham risk score is heavily dependent on age, which underestimates CV risk in young individuals [26] as shown in studies.

CAD is an overt manifestation of atherosclerosis. Atherosclerosis being a generalized process affects all the vessels. Thus, many patients with CAD develop other complications of atherosclerosis, one being the Peripheral Artery Disease (PAD). Patients with PAD have attenuated flow-mediated dilatation of the brachial artery, which suggests the loss of nitric oxide activity [27]. Thus, atherosclerosis forms a common basis of impairment of endothelium function, increased thickness of carotid intima and PAD. In this present study, a highly significant negative correlation (r= -0.220, p=0.005) was found between FMD and CIMT among all the subjects (cases and control). In all subjects together (cases and controls), Erzen et al [10] also found a significant negative correlation between FMD and CIMT. In our study, a highly significant positive correlation was also found between FMD and ABI among cases and control groups. A statistically significant negative correlation was found between endothelial dependent FMD and PP among cases and control groups. These results were significant despite six weeks of regular medications for CAD which might have improved endothelial function in these patients.

A multivariate regression analysis was done between various risk factors and FMD, CIMT and ABI among cases. However, none of the risk factor correlated with these biophysical parameters significantly. Thus, these risk factors in our cases did not contribute significantly to FMD, CIMT, ABI and PP and thus to the atherosclerotic process. Thus taking controls with no risk factors did not create a bias to the values of FMD, CIMT, ABI and PP.

Some authors have measured endothelial dysfunction as an additional marker of coronary risk. They estimated the risk on the basis of endothelial dysfunction and found that endothelial dysfunction has a higher predictive value than risk estimated from the presence of classical risk factors [28-30].

Questions to be answered

1. Can these biophysical parameters be used to predict the future cardiovascular events among the young population?
2. Does the Framingham risk score truly predict the risk of developing CAD in young male patients with various risk factors especially among the Indians?
3. Do we need more aggressive therapy for the patients of CAD for the early normalization of the markers of atherosclerosis and endothelial dysfunction?
4. Can we follow-up the patients of CAD with these biophysical parameters?
5. Can these biophysical parameters be used for risk scoring for CAD in addition to Framingham risk score in young Indian population?

LIMITATION

Our study was having small number of subjects and was conducted at one centre only. There was a short follow-up. Radiological assessment was made by a single radiologist. In future, studies can be planned to find answers to the above questions.

CONCLUSION

In this study we observed that there was a significant difference of various biophysical parameters (FMD, CIMT, ABI and PP) among young patients of CAD and healthy controls. FMD was found to have a negative correlation with CIMT and PP among all subjects. Deterioration of FMD correlated with the deterioration of ABI. Despite the positive effect of drugs for treatment of CAD on biophysical parameters the results (FMD, CIMT, ABI and PP) were still aberrant from healthy controls. Majority of our young male patients fell in low risk Framingham risk score but they still developed CAD. Screening by these biophysical parameters (FMD, CIMT and ABI) may also be useful to predict the cardiovascular risk in addition to Framingham risk score in highly predisposed young Indian population. Various risk factors for CAD did not contribute significantly to the atherosclerotic process.

REFERENCES

[1] Ghaffar A, Reddy KS, Singhi M. Burden of non-communicable diseases in South Asia. *BMJ*. 2004;328(7443):807-10.
[2] Enas EA, Dhawan J, Petkar S. Coronary artery disease in Asian Indians: lessons learnt and the role of lipoprotein (a). *Indian Heart J*. 1997;49(1):25-34.
[3] Harding S. Mortality of migrants from the Indian subcontinent to England and wales: effect of duration of residence. *Epidemiol*. 2003;14:287-92.
[4] Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340(8828):1111-15.
[5] Peretz A, Leotta DF, Sullivan JH, Trenga CA, Sands FN, Aulet MR, et al. Flow mediated dilation of the brachial artery: an investigation of methods requiring further standardization. BMC *Cardiovascular Disorders*. 2007;7:11.
[6] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness a systematic review and meta-analysis. *Circulation.* 2007;115:459-67.
[7] Tsai AW, Folsom AR, Rosamond WD, Jones DW. Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. *Stroke*. 2001; 32: 1721–24.
[8] Yuanxi XU, Jue LI, Yingyi LUO, Yongquan Wu, Liqiang Zheng, Jinming Yu, et al. The association between ankle-brachial index and cardiovascular or all-cause mortality in metabolic syndrome of elderly Chinese. *Hypertens Res*. 2007;30(7):613-19.
[9] Kweon SS, Shin MH, Park KS, Nam HS, Jeong SK, Ryu SY, et al: Distribution of the ankle-brachial index and associated cardiovascular risk factors in a population of middle-aged and elderly Koreans. *J Korean Med Sci*. 2005;20:373–78.
[10] Erzen B, Sabovič M, Poredos MSP. Endothelial dysfunction, intima-media thickness, ankle-brachial pressure index, and pulse pressure in young post-myocardial infarction patients with various expressions of classical risk factors. *Heart Vessels*. 2007; 22:215–22.
[11] Iribarren C, Go AS, Husson G, Sidney S, Fair JM, Quertermous T, et al. Metabolic syndrome and early onset coronary artery disease: is this whole greater than its parts? *J Am Coll Cardiol*. 2006;48(9):1800-07.
[12] Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al: Definition of myocardial infarction—a global consensus document of The Joint ESC/ACC/AHA/WHF/WHO Task Force for the Redefinition of Myocardial Infarction, 2007.
[13] Corretti MC, Anderson TJ, Benjamin EJ,Celermajer D, Charbonneau F, Creager MA, et al . Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol*. 2002; 39(2): 257-65.
[14] Al-Qaisi M, Nott DM, King DH, Kaddoura S. Ankle brachial pressure index (ABPI): An update for practitioners. *Vasc Health Risk Manag*. 2009;5:833-41.
[15] Narsingan SN. Premature atherosclerosis - Indian scenario. In (AK Das editor) *Postgraduate medicine* 15th ed. New Delhi: APICON. 2001:119-29.
[16] Rissam HS, Kishore S, Trehan N. Coronary artery disease in young Indians – the missing link. *Journal, Indian Academy of Clinical Medicine*. 2001:2(3);128-32.
[17] Tewari S, Garg N, Kapoor A, Jain A, Singh U, Godbole MM, et al. Association of common carotid intimal media thickness and lipoprotein(a) with coronary artery disease. *Indian Heart J*. 2004;56:642-45.

[18] Kasliwal RR, Bansal M, Gupta H, Agarwal S. Association of carotid intima-media thickness with left main coronary artery disease. *Indian Heart J*. 2007;59:50-55.
[19] Otikunta Adikesava Naidu, Durgaprasad Rajasekhar, SAA Latheef. Assessment of endothelial function by brachial artery flow mediated dilatation in microvascular disease. *Cardiovasc Ultrasound*. 2011; 9: 40.
[20] Ray KK, Cannon CP. Intensive statin therapy in acute coronary syndromes: clinical benefits and vascular biology. *Curr Opin Lipidol*. 2004;15:637–43.
[21] Tsiara S, Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. *Curr Med Res Opin*. 2003;19:540–56.
[22] Premlatha G, Shanthirani S, Deepa R, Markovitz J, Mohan V. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population. *Diabetes Care*. 2000;23:1295–1300.
[23] Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham Heart Study. *Circulation*. 1999;100(4):354–60.
[24] Berne RM, Levy MN. Cardiovascular Physiology. St Louis, Mo: CV Mosby; 1992:113–144.
[25] Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, et al. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. *Circulation.* 1997;96:4254–60.
[26] Hemann BA, Bimson WF, Taylor AJ. The Framingham risk score: an appraisal of its benefits and limitations. *Am Heart Hosp J*. 2007;5:91-96.
[27] Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. *Circulation*. 2011;123(1):87-97.
[28] Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168–75.
[29] Anderson TJ. Nitric oxide, atherosclerosis and the clinical relevance of endothelial dysfunction. *Heart Fail Rev*. 2003;8:71–86.
[30] Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002;106:653–58.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Rheumatology, CMC, Vellore, Tamilnadu, India.
2. Professor, Department of Medicine, University College of Medical Sciences, Dilshad Garden, Delhi, India.
3. Professor, Department of Radio-Diagnosis, University College of Medical Sciences, Dilshad Garden, Delhi, India.
4. Professor, Department of Medicine, University College of Medical Sciences, Dilshad Garden, Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Nikhil Gupta,
Senior Resident, Department of Rheumatology, CMC, Vellore, Tamilnadu, India.
Email: drnikhilguptamamc@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 21, 2016**
Date of Peer Review: **Jul 01, 2016**
Date of Acceptance: **Jul 12, 2016**
Date of Publishing: **Oct 01, 2016**