Original Article

Endothelial dysfunction and the role of hypertension in Nepalese subjects with major coronary risk factors

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Abstract

Background and Aims: Hypertension is one of the major coronary heart disease risk factors. Endothelial dysfunction is thought to be the preclinical vascular changes in the pathogenesis of atherosclerosis and it its major manifestation; coronary heart disease. This study was designed to assess the endothelial function in subjects with major coronary risk factors including hypertension.

Methods: The study was conducted in a tertiary referral centre in Central Nepal. A cross-sectional study was conducted on the cohort of 100 subjects with at least one out of six major coronary heart disease risk factors. JNC 7 criteria were used to define hypertension. Brachial artery flow-mediated dilation was measured using high-resolution ultrasound. Endothelial dysfunction was defined as flow-mediated dilation value <9.99%. The association between endothelial dysfunction and hypertension was assessed by univariate and multivariate analysis.

Results: Out of 100 subjects with coronary risk factors (mean age 46.75±9.95 years, mean number of risk factors 2.81±1.17), 65% subjects were hypertensive and 35% were non-hypertensive. Hypertension as a risk factor was evident in 80.39% and 48.98% subjects with abnormal and normal endothelial response respectively (p = 0.001). In addition, 63.08% and 28.57% subjects with and without hypertension had endothelial dysfunction respectively (p = 0.01). Hypertension was the only coronary risk factor associated with endothelial dysfunction in a multivariate model (p = 0.04).

Conclusion: Hypertension was strongly associated with endothelial dysfunction and it could be the best predictor of endothelial dysfunction and subsequent coronary heart disease in coronary heart diseases risk factor cohorts.

Key words: Hypertension, endothelial dysfunction, coronary risk factors

Introduction

Hypertension is the most common condition predisposing to coronary heart disease. The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) report identified the hypertension as a risk factor for cardiovascular disease.[1] It is readily identifiable reversible risk factor and its burden is rising and projected to affect one third of the world's population by the year 2025. Currently, high blood pressure (BP) causes about 54% of stroke and 47% of coronary heart disease (CHD) worldwide.[2]

Endothelial dysfunction (ED) is thought to be the preclinical vascular changes in the pathogenesis of atherosclerosis including systemic hypertension and coronary heart disease. Alteration in endothelial function and impaired balance between endothelial relaxing and constricting factors play an important role in the pathogenesis of atherosclerosis.[3] ED is both an early marker of vascular disease and a precursor in the development of atherosclerosis.[4,5] Studies have shown that the presence of endothelial dysfunction identifies individuals at increased risk for cardiovascular disease events. [6,7,8,9]

Coronary artery disease is associated with endothelial dysfunction which can be diagnosed preclinically.[10] ED, defined by a lower flow-mediated dilation (FMD) value, has been found to be associated with cardiovascular events.[11] The brachial-artery flow-mediated dilation (FMD) has been extensively used to identify the ED proposed as a surrogate marker of cardiovascular disease.[12,13,14] Studies have reported diverse association between HTN and ED. Brunner et al and others reported the presence of endothelial dysfunction in hypertensive subjects.[15,16,17] In contrast to this, Cockcroft et al had reported normal endothelial function in hypertensive subjects.[18]

This study was designed to assess the endothelial function in subjects with various coronary risk factors including hypertension.

Methods

The study was conducted in College of Medical Sciences – Teaching Hospital, Bharatpur, a tertiary referral centre. A cross-

sectional study was designed. A cohort of 100 subjects with at least one out of six major CHD risk factors: hypertension, diabetes, obesity, age more than 45 years in male and more than 55 years in female, dyslipidemia and smoking were selected. The subjects with major coronary risk factors without obvious coronary heart disease and definitive structural and functional heart diseases were included in the study cohort. JNC 7 criteria were used to define hypertension - any blood pressure level on treatment for hypertension and the blood pressure more or equal to 140/90 mmHg in two separate readings taken at least 1 week apart in those without treatment.[19] Other CHD risk factors were defined as per the Adult Treatment Panel – III;[1] diabetes was defined as the subjects on treatment for diabetes or fasting plasma glucose more or equal to 126 mg/dl, or postprandial plasma glucose level more or equal to 200 mg/dl or random blood sugar level more or equal to 200 mg/dl in the presence of symptoms suggestive of raised blood sugar level. Similarly dyslipidemia was defined as any one of the following – LDL more than 130 mg/dl or HDL less than 40 mg/dl.[1] Any subjects with age 20 to 70 years, having at least one major CHD risk factor mentioned above and clinically stable were included in the cohort. Subjects with coronary heart disease, terminal illness, any other active illness and regularly taking medicines having effect on endothelial function such as statins, ACE inhibitors were excluded from the study. The study was approved by Institutional Review Board. An informed consent was taken from each patient and the required information was recorded as per predefined performa.

Each subject had undergone detail clinical evaluation followed by basic and advanced biochemical and haematological laboratory tests including renal, liver and thyroid function test and lipid profile. In addition, these subjects were also undergone non-invasive comprehensive cardiac evaluation including electrocardiography and echocardiography to rule out coronary heart disease and advanced cardiac conditions. Brachial artery flow-mediated dilation was measured using high-resolution ultrasound as described elsewhere.[20,21] After a 15-min resting period in a air-conditioned room (22°C to 25°C), the FMD was assessed in the subject's right arm in the recumbent position by ACUSON 300, Premium Edition (SIEMENS, Germany) with a 10.1 MHz linear array transducer. The brachial artery was imaged and the diameter at end diastole was measured. Three readings of brachial artery diameter were taken and mean was calculated which was the baseline diameter. A pressure cuff was placed on the forearm distal to the target artery and it was inflated to at least 50 mm Hg above systolic pressure until no blood flow was detected through the brachial artery with the Doppler probe for 5 minutes. After 5 min, the cuff was released, and the diameter of the brachial artery was measured at 30, 60, 90 and 120 seconds. The second reading i.e. 60 seconds measurement was taken to calculate the change in brachial artery diameter and it was expressed in percentages.

The study was analysed in a case-control fashion. The cohort was divided in two group based on the presence of hypertension. The cases included subjects with hypertension and remaining subjects were taken as controls and comparison was made between them. Endothelial dysfunction was defined as flow-mediated dilation value <9.99%.[22,23] Based on the presence of endothelial dysfunction the subjects were also divided into two groups with and without ED and various parameters were compared between them. The various confounding factors in hypertensive and non-hypertensive groups were analysed. In addition, similar comparison was also made between subjects with and without ED.

Data were analysed by using SPSS 17.0. The categorical data were expressed in percentages and analyzed using χ^2 test. Continuous data were presented in the form of mean with standard deviation and the significance of difference between two means was tested by using student t test. The association between endothelial dysfunction and hypertension was assessed by univariate and multivariate analysis.

Results

One hundred subjects with various coronary risk factors were selected and studied (Figure 1). Mean age was 46.75±9.95 years. The mean number of coronary risk factors on these subjects was 2.81±1.17. Majority of the subjects (65%) were hypertensive. The proportion of subjects with other risk factors was: DM - 11%, Smoking – 19%, Age (Men >45, Women > 55) – 44%, BMI High risk (> 27.5 Kg/m2) – 66% and Dyslipidemia - 81% (Table 1).

Hypertension as a risk factor was evident in 80.39% and 48.98% subjects with abnormal and normal endothelial response respectively (p = 0.001). In addition, 63.08% and 28.57% subjects with and without hypertension had endothelial dysfunction respectively (p = 0.01).

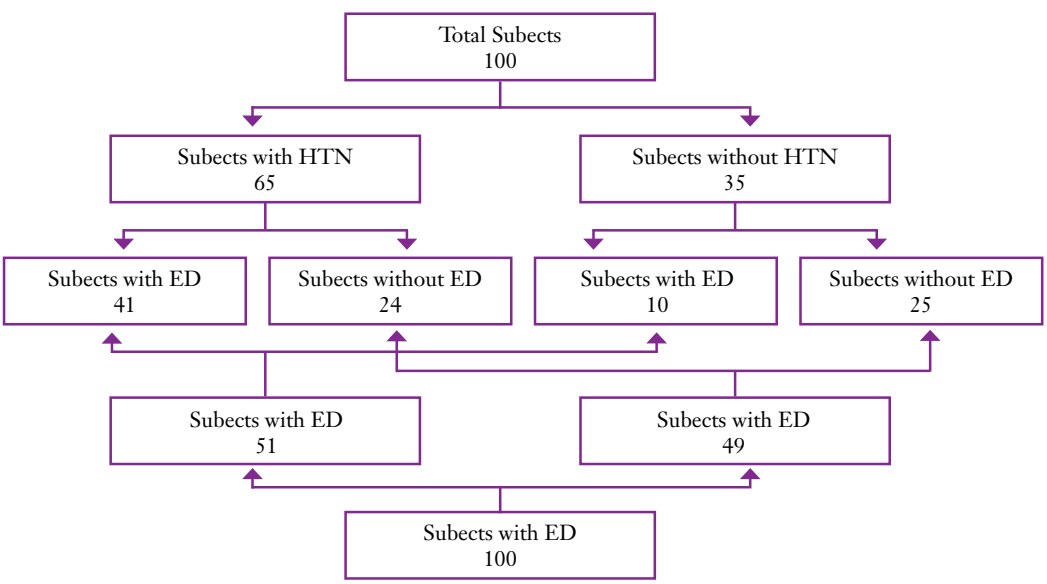

Fig. 1. Study subjects. HTN, Hypertension, ED, Endothelial dysfunction

Table 1. Studied parameters in subjects with and without hypertension (HTN)

Parameters	Subjects with HTN N = 65	Subjects without HTN N = 35	P value
Age (Years)	49.8±8.85	41.09 ± 9.47	<0.001
Male	33 (50.77)	9 (25.71)	0.01
Change in BAD (mm)	0.34± 0.19	0.43± 0.16	0.02
FMD	8.77± 4.75	12.1± 4.3	0.01
Endothelial dysfunction (%)	41 (63.08)	10 (28.57)	0.01
Number of CHD risk factors	3.23±1.15	2.06±0.68	<0.001

Table 2. Endothelial function parameters in subjects with and without endothelial dysfunction.

Parameters	Subjects with ED N = 51	Subjects without ED N = 49	p Value
Mean Age (yrs)	50.57±98.94	42.78±9.44	<0.001
Male (%)	27 (52.94)	15 (30.61)	0.02
Mean increase in BAD (mm)	0.23±0.13	0.51±0.08	NA
Mean FMD	5.85±2.75	14.06 ± 1.94	NA
Mean number of risk factors	3.43±1.04	2.18±0.86	<0.001
Number of CHD risk factors	3.23±1.15	2.06±0.68	<0.001

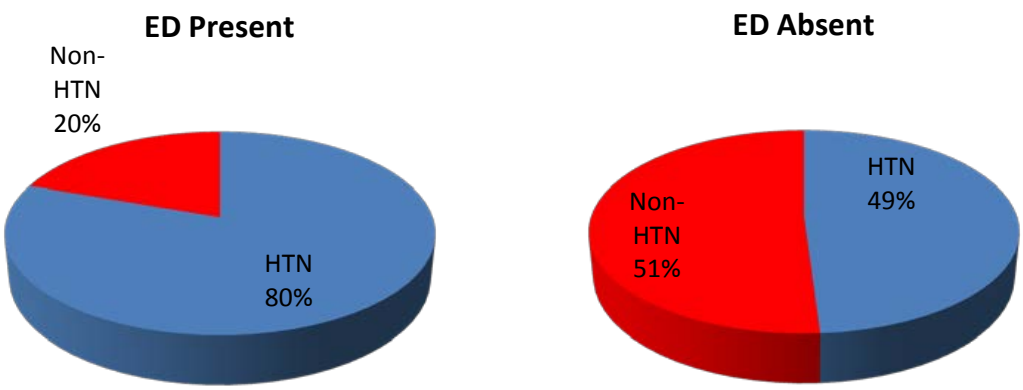

Figure 2. Endothelial function (ED) in subjects with and without hypertension (HTN)

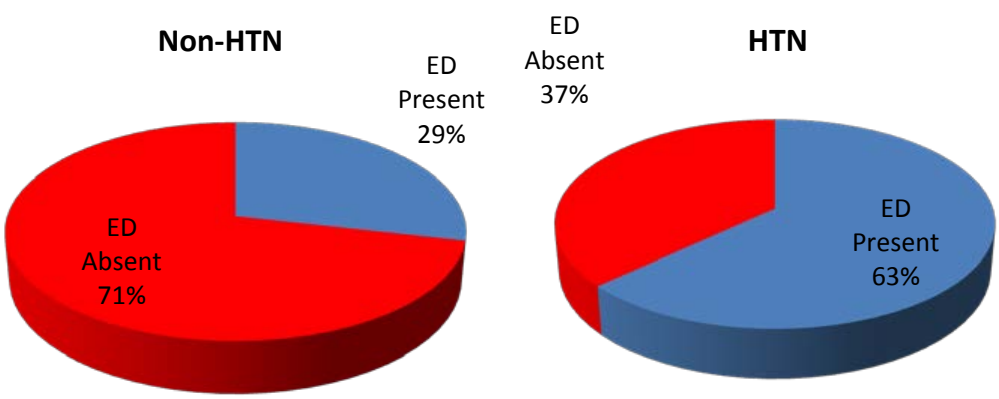

Figure 3. Hypertension in subjects with and without endothelial dysfunction

Table 3: Univariate association between risk factors and endothelial dysfunction defined as FMD ≤ 9.99% in study subjects

	OR	CI (95%)	P value
Age (yrs)	1.09	1.044-1.149	<0.001
Smoking	0.3	0.099-0.912	0.03
Dyslipidemia	4.05	1.34 -12.25	0.01
Diabetes	5.7	1.18 -27.6	0.03
Hypertension	4.27	1.35-10.39	0.001
BMI of High Risk	1.16	0.52-2.59	0.71

Table 4: Multivariate association between risk factors and endothelial dysfunction defined as FMD ≤ 9.99% in study subjects.

	OR	CI (95%)	P value
HTN	6.436	1.067-38.809	0.042
DM	11.463	0.272-483.962	0.202
Smoking	1.127	0.056-22.517	0.938
Sex	1.749	0.284-10.759	0.547
Dyslipidemia	2.905	0.277-30.483	0.374
Age	0.890	0.092-8.578	0.920

In a subanalysis where all subjects were divided in tertiles according to FMD values, the rate of hypertension was falling from 87.88% to 63.64% to 44.12% in subjects in lower, middle and upper tertiles respectively. Hypertension was associated with ED in univariate analysis (OR 4.27, CI 1.35-10.39 p = 0.001). Other CHD risk factors such as diabetes, smoking, age, and dyslipidemia were also associated with ED in univariate analysis (p < 0.05). But high risk BMI including obesity and abdominal obesity were not associated with ED even in univariate analysis (p = 0.71 and 0.68). In multivariate analysis where the role of various confounding factors was considered, hypertension was the only CHD risk factor associated with ED (OR 6.436, CI 1.067-38.809, p = 0.042). Association of ED with other risk factors was not statistically significant.

Discussion

Various studies have shown that both the hypertension and endothelial dysfunction are risk factors and provide additive prognostic values in predicting cardiovascular events.[11] In our study, the rate of endothelial dysfunction was 63.08% and 28.57% in hypertensive and non-hypertensive subjects respectively (p = 0.01). Similarly, the rate of hypertension was 80.39% and 48.98% in subjects with and without endothelial dysfunction (p = 0.001). Brunner H et al,[15] Benjamin EJ et al,[16] and Felmeden DC et al[17] also has reported similar association between HTN and ED in their study. There are reports showing the predictive power of endothelial dysfunction for the development of hypertension in future. Rossi et al. had suggested that the presence of endothelial dysfunction can increase the susceptibility to develop hypertension and diabetes.[24] Similar association between ED and HTN was also seen in the Framingham cohort analysis of 2883 individuals (53% female) using FMD as a measure of endothelial function.[16]

In our study, the rate of endothelial dysfunction was 63.08% and 28.57% in hypertensive and non-hypertensive subjects respectively (OR=4.2, p = 0.01). Similarly, the rate of hypertension was 80.39% and subjects were divided in tertiles according to FMD values, the rate of hypertension was falling from 87.88% to 63.64% to 44.12% in subjects in lower, middle and upper tertiles respectively. It showed strong relationship between hypertension and endothelial dysfunction. Moreover, the hypertension as a CHD risk factor was the only factor having strong power as a predictor of ED. It was significantly associated with ED in univariate (OR 4.27, CI 1.35-10.39 p = 0.001) and multivariate analysis (OR 6.436, CI 1.067-38.809, p = 0.042). Similar findings of the presence of endothelial dysfunction in hypertensive subjects was also reported by Brunner et al.[15] and others.[16,17] Benjamin et al[16] examined a measure of endothelial function, brachial artery flow-mediated dilation (FMD), expressed as both percent (FMD%) and actual dilation by ultrasound with the occlusion cuff below the elbow in 2883 Framingham Study participants (52.9% women; mean age, 61 years). They concluded that the increasing age, systolic blood pressure, BMI, and smoking were associated with lower FMD% in the community-based sample, whereas prior exercise and increasing heart rate were associated with higher FMD%. Thus the Framingham cohort analysis has clearly demonstrated a relationship with blood pressure and other CHD risk factors.[16] Felmeden et al[17] had studied 84 hypertensive patients (74 men; mean age, 64 years; SD 8) by calculating an LDL score, with higher scores being equivalent to a greater proportion of the more atherogenic LDL subfractions. High-resolution ultrasound was used to assess endothelium-dependent brachial artery FMD after reactive hyperemia after vessel occlusion. Baseline levels were compared with 61 age- and gender-matched healthy normotensive control subjects. Mean LDL score was higher and FMD impaired in hypertensive subjects compared with control subjects.

In contrast to this, Cockcroft et al.[18] had reported normal endothelial function in hypertensive subjects. They had reassessed this issue by measuring forearm blood flow by plethysmography during the infusion of vasodilators into the brachial arteries of 95 subjects: 37 normotensive controls and 58 patients with essential hypertension. They recorded that the vasodilator responses to nitroprusside, acetylcholine, carbachol, and isoproterenol were also similar in separate groups of normotensive controls and hypertensive subjects, whether the subjects had never been treated for hypertension or had had therapy withheld for two weeks. In contrast to previous studies, their findings suggest that selective impairment of the responsiveness of the forearm vasculature to muscarinic agonists is not universal in patients with essential hypertension.

However, there are reports showing not only endothelial dysfunction in hypertensive subjects but also the predictive power of endothelial dysfunction for the development of hypertension in future. Rossi et al.[25] had suggested that the presence of endothelial dysfunction can increase the susceptibility to develop hypertension and thus hypertension can be seen not only as a collateral feature of established risk factors, but also a possible pathogenetic mechanism for their onset. Chang et al conducted a study in subjects having exercise-induced hypertension to clarify whether this condition is related to endothelial dysfunction or not by evaluating the endothelial function of the brachial artery with high-resolution ultrasound technique,[25] and measuring the concentration of NO2/NO3 and cyclic guanosine monophosphate (GMP).[26] They concluded that patients with exercise-induced hypertension have impaired endothelium-dependent vasodilatation and the endothelial dysfunction may play an important role in exercise-induced hypertension. They also proposed that the patients with exercise-induced hypertension have poor endothelial dependent vasodilatation due to an impaired nitric oxide /cyclic GMP pathway and this might play a significant role in increasing blood pressure during exercise with inadequate peripheral adjustment to changing cardiac output.

In overall, despite some contrast reports regarding the association of hypertension and endothelial dysfunction, majorities are in the favour of the deleterious effects of hypertension on endothelial function and our findings are also in accordance with these observations. Further study with large sample size and design to assess causal relationship between hypertension and endothelial dysfunction could be more informative and can further clarify the issue.

This Study was designed to assess the association between ED and HTN; therefore, a causal relationship cannot be drawn. All the subjects had at least one (up to six) major CHD risk factors and comparison was made with the subjects having other CHD risk factors, therefore the effect of other risk factors in endothelial function might have interference in the analysis. Another important limitation in this study was the bias caused by cardiology OPD based enrollment of the study subjects. This could be the reason for the higher proportion of hypertensive subjects in the study cohort. Moreover, in the logistic regression models although final outcome with the multivariate analysis does show a significant Odds with the hypertensive for endothelial dysfunction and a significant P value, this only signified a statistical significance and not a very strong clinical significance due to a wide ranging confidence interval (CI). This must be noted while interpreting the study and drawing a conclusion. Similarly, the small sample size and cross-sectional nature of the study with its inherent limitations should be taken in consideration while generalizing these findings.

Conclusions

Among the studied coronary risk factors, hypertension, diabetes, smoking, age, dyslipidemia were associated with endothelial dysfunction – a surrogate marker, precursor or risk factor of CHD as shown in univariate analysis. The study was unable to establish the association of other coronary risk factors and endothelial dysfunction. Among these coronary risk factors only the hypertension was strongly associated as shown in univariate as well as in multivariate analysis, with endothelial dysfunction and could be the strong and best predictor of endothelial dysfunction and subsequent coronary heart disease. But the wide ranging confidence interval in this association should be taken in consideration while interpreting the present study and needs on further research with appropriate design and methodology.

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