

Original Research Article

Association of Carotid Intimal Thickness with Fibrinogen & CRP in Diabetic Hypertensives

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Abstract: Diabetes and hypertension are two major diseases which account heavily for overall mortality and morbidity. Various associations have been studied between diabetes and hypertension with different markers to diagnose and assess the severity of these diseases. However, in current scenario carotid intimal thickness, fibrinogen and CRP have been most sought after. Not only these markers help in assessing the disease but also provide a lead to prognosis. The objective is to find association of Carotid Intimal thickness with fibrinogen and CRP in Diabetic Hypertensives. This was a prospective, non-interventional cross sectional study. Subjects were identified using inclusion criteria and investigations were done using standard guidelines. Patient privacy and confidentiality was maintained. In this study CRP was found significantly high in diabetic hypertensives. Fibrinogen was found significantly high in diabetic hypertensives. Carotid intimal thickness was on higher side in diabetic hypertensives. There was significant association between CRP and carotid intimal thickness in diabetic hypertensives. There was significant association between Fibrinogen and carotid intimal thickness in diabetic hypertensives. From this study we can conclude that there is a significant association of markers of inflammation CRP and fibrinogen with carotid intimal thickness in diabetic hypertensives.

Keywords: Diabetes, Hypertension, Carotid Intimal thickness, Fibrinogen, CRP

INTRODUCTION:

Hypertension and diabetes, two of the major global risks for mortality, [1] are on a rapid rise in developing nations. In India, as per the 2011 estimates reported by the Indian Council of Medical Research–India Diabetes study, 62.4 and 77.2 million people had diabetes and prediabetes, respectively [2]. It is predicted that by 2030, India's diabetes burden will be almost 87 million people [3]. Moreover, there is an increasing prevalence of hypertension in the Indian population, especially in the urban areas [4]. Diabetes and elevated blood pressure (BP) have been linked to ischemic heart disease, peripheral vascular diseases, stroke, myocardial infarction, and renal failure. Hypertension and diabetes are important risk factors for cardiovascular disease. Given the increasing rates of coronary artery disease among Indians, especially at a younger age, [5] understanding and successfully managing hypertension and diabetes is essential to reducing cardiovascular mortality in India.

Diabetes and hypertension are known to coexist in patients. The prevalence of hypertension is 1.5–2.0 times more in those with diabetes than in those without diabetes, almost one-third of the patients with hypertension develop diabetes later [6]. This coexistence presents an increased risk and can accelerate vascular complications like atherosclerosis. Both diabetes and hypertension are risk factors for atherosclerosis and their simultaneous presence hastens the pathogenesis of atherosclerosis [7, 8]. Evidence suggests that thrombosis, endothelial dysfunction and inflammation are strongly associated with coronary artery disease (CAD). Inflammation plays a crucial role in characterizing the formation of atheromatous plaque, as well as its progress [9, 10]. The role of atherosclerosis has been proven beyond doubt in coronary artery disease, cerebrovascular disease and peripheral vascular disease.

As various studies have already proved that atherosclerosis is a generalized process involving most

of the major arteries at a time and has a silent course it is important to recognize the process early to prevent diseases like myocardial infarction, stroke and peripheral gangrene [11, 12]. When atherosclerosis reaches symptomatic stage the disease already has major and poorly reversible histopathological consequences. Atherosclerosis progression is associated with inflammatory changes from its early stages to the most advanced, accompanied by thrombotic events [13].

As it has been already proved that atherosclerosis and inflammation are interlinked and it is of utmost importance to identify early markers for the disease, such as inflammatory factors identifiable in serum or endothelial dysfunction and thickening in order to prevent disease progression. Carotid intima-media thickness (CIMT) is such a marker that can be used to identify subclinical atherosclerotic disease. Because it can be measured in a relatively simple and non-invasive way, it is well suited for use in large-scale population studies [14].

Inflammation mediates pathogenesis of atherosclerosis and thus various markers of inflammation are being studied vigorously to see whether they can be used to diagnose atherosclerosis at an early stage. C-reactive protein and fibrinogen are among these inflammatory mediators [15,16].

Despite the literature supporting a role of fibrinogen as a marker of CAD and its consequences, several studies have investigated the role of fibrinogen as a risk factor mediator of CAD. Shojaie *et al.*; [17] and Pineda *et al.*; [18] introduced high levels of fibrinogen as a risk factor for premature CAD in subjects <55 years.

A role in subclinical atherosclerosis has been attributed to this acute phase protein, as higher levels of fibrinogen during young adulthood were positively associated with prevalence of coronary artery calcification and increased carotid intimal-medial thickness in middle age [19].

Fibrinogen and CRP levels have been established as strong predictors of subclinical atherosclerosis associated with an extension of carotid atherosclerosis in hypertensives [20]. Supporting data has previously shown that fibrinogen is involved in the subclinical phase of extra coronary and coronary atherosclerosis and may add to the atherogenic effect of hyperlipidemia [21]. Fibrinogen levels have been found to be independently related to cardiovascular mortality, extent, [22] as well as the severity of disease [23].

MATERIAL AND METHODS:

The present study entitled "Association of

carotid intimal thickness with fibrinogen and CRP in diabetic hypertensives" was carried out in the Department of Cardiology, Choithram Hospital and Research Centre, Indore, on patients suffering from diabetes as well as hypertension of age more than 18 years of either sex. Study was done after clearance from institutional ethical and scientific committee and obtaining informed consent from the study subjects as per proforma.

Study Design

The present study is a prospective, non-interventional, observational study.

Study Period

One year from 01-Jul-2014 to 30-Jul-2015.

Study Population

Patients visiting the IPD/OPD at Choithram Hospital & Research Centre, Indore (M.P.) during the study period will form the study population.

Sample Size

To determine the coefficient correlation of 0.6 between fibrinogen level and carotid intima media thickness, a sample size of 16 would be required, at power of 80%. Hence, we have included 30 patients in our study.

Inclusion Criteria

- Patients suffering from both diabetes and hypertension.
- Patients more than 18 years of age of either sex.
- Patients suffering from both diabetes and hypertension for more than 6 months.
- Patient and / or his/her legally acceptable representative willing to provide voluntary written informed consent for participation in the study.

Exclusion Criteria

- Patients with concomitant medical disorders like connective tissue disorders, liver diseases effecting serum levels of CRP and fibrinogen level.
- Patients having temperature >37.7°C which may be due to an inflammatory process effecting levels of CRP and fibrinogen.
- Patient and / or his/her legally acceptable representative not willing to provide voluntary written informed consent for participation in the study.

METHODOLOGY

Diabetic and hypertensive patients:

Diabetes will be labelled as per the guidelines of American diabetes association, European association for the study of diabetes and the international diabetes federation which states:

If any one of the following criteria is satisfied the person can be labelled as diabetic:

1. Symptoms of diabetes plus random blood glucose concentration more than or equal to 11.1 mmol/L (200 mg/dl)
2. Fasting plasma glucose more than or equal to 7.0 mmol/l (126 mg/dl)
3. Glycosylated haemoglobin more than 6.5%
4. Two hour plasma glucose more than or equal to 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test.

Hypertension will be labelled to people having systolic blood pressure of >140 and a diastolic blood pressure of >90. All selected OPD and IPD patients belonging to study period fulfilling selection criteria were included after obtaining informed consent as per proforma. The evaluation comprised of detailed clinical history and a thorough general physical examination and relevant investigations. Once the diagnosis of diabetes and hypertension is made, carotid intimal thickness, serum fibrinogen and CRP levels were measured as per the proforma.

In the present work the investigations done were:

- Measurement of carotid intimal thickness
- Measurement of serum levels of CRP and fibrinogen

To visualize the common carotid artery in its full length, without overlapping, two methodological approaches were used. In the first, to determine the thickness of common carotid arteries a standardized scanning technique was developed.

Scanning of extra cranial carotid arteries in the neck will be performed in three different projections anterior and posterior [patient lying on his/her back with the head in axis] and lateral [head turned 45° contralateral to the carotid artery under examination]. For each projection the carotid will be identified at the level of the bifurcation and scanned in a craniocaudal direction. To avoid overlapping the probe will be placed along the common carotid artery, with anatomic internal points of reference displayed on the monitor (i.e., echogenic structure present in the muscles)

Measurement of CRP by Turbidimetry

The latex particles coated with anti-CRP are agglutinated when they react with samples that contain low levels of C-reactive protein (CRP). The latex particles agglutination is proportional to the concentration of the CRP in the sample and can be measured by turbidimetry.

Measurement of Fibrinogen by Turbidimetry

A turbidimetric micro method for estimation of

fibrinogen, both manual and by automatic analysis is described. It is based on the use of a reagent containing ammonium sulphate, EDTA and glycerol. The blood may be collected either on heparin, EDTA or trisodium citrate. The correlation with the weight methods ($r=0.980$), chromometric methods ($r = 0.939$) and immunonephelometric methods ($r=0.985$) permits its use as a routine method.

Statistical Methods

To find out the correlation between the two parametric data, Pearson's coefficient of correlation 'r' was used. A P value of < 0.05 was considered to be significant. The statistical package SPSS Version 20.0 was used for analysing data. The data in the final report was represented using tables and graphs.

RESULT AND ANALYSIS:

In the present study there are total 30 participants of which 1 (3.33%) participant is from age group 41 to 50 years 7 (23.33%) were from age group 51 to 60 years, 9 (30%) were from age group 61 to 70 years, 12 (40%) were from age group 71 to 80 years and 1 (3.33%) was more than 80 years.

The mean fasting blood sugar in seven females was 168.43 ± 16.81 mg/dL and in twenty-three males was 214.39 ± 46.59 mg/dL. Overall mean value of fasting blood sugar was 203.67 ± 45.78 mg/dL. In females the mean systolic blood pressure was 158.00 ± 4.16 mm Hg and in males it was 158.00 ± 4.16 mm Hg, while in all the participants the mean was 165.80 ± 11.45 mm Hg. In females the mean diastolic blood pressure is 88.29 ± 7.70 mm Hg and in males it was 85.39 ± 9.68 mm Hg. The overall mean was 86.07 ± 9.21 mm Hg.

In females the mean C-IMT is 0.79 ± 0.08 cm, in males 0.82 ± 0.08 cm and the mean in all the participants is 0.81 ± 0.08 cm. In females the mean fibrinogen level is 324.10 ± 151.40 mg/dL in males it is 314.20 ± 90.20 mg/dL while mean in total participants is 316.50 ± 104.60 mg/dL. In females the mean CRP level is 71.90 ± 43.60 mg/L, in males it is 73.04 ± 35.08 mg/L, the mean in total participants is 72.78 ± 36.43 mg/L.

Pearson correlation coefficient 'r' between Fibrinogen and C-IMT was found to be 0.390 and P value was 0.033, which is statistically significant. Thus, there is a statistically significant positive correlation between Fibrinogen and C-IMT.

Pearson correlation coefficient 'r' between CRP and C-IMT was found to be 0.584 and P value was 0.001, which is statistically significant. Thus, there is a statistically significant positive correlation between CRP and C-IMT.

Table 1: Distribution of Patients According to Age
(N=30)

Age Group	Number	Percentage	CIMT (Mean±SD)
40-50 years	1	3.33	0.70 ± 0.00
51-60 years	7	23.33	0.83 ± 0.08
61-70 years	9	30.00	0.78 ± 0.07
71-80 years	12	40.00	0.84 ± 0.08
>80 years	1	3.33	0.90 ± 0.00
Total	30	100.00	0.81 ± 0.08

Table 2: Mean C-IMT According to Gender (N=30)

Parameter	Female (N=7)	Male (N=23)	Overall
C-IMT (mm)	0.79 ± 0.08	0.82 ± 0.08	0.81 ± 0.08
Fibrinogen (mg/dL)	324.10 ± 151.40	314.20 ± 90.20	316.50 ± 104.60
CRP Level (mg/L)	71.90 ± 43.60	73.04 ± 35.08	72.78 ± 36.43

DISCUSSION:

Diabetes and hypertension are major health problems in India which are increasing in prevalence at a lightning speed. Mortality in both the diseases is mainly due to atherosclerosis which can result in CVD, cardiovascular disease and peripheral artery disease. This study is an effort to investigate whether inflammatory markers can be used to ascertain the burden of atherosclerosis in these patients and if at all they can help in early diagnosis, so that the atherosclerotic process can be intervened at an earlier stage.

The present study has been carried out in 30 diabetic hypertensives (indoor and outdoor patients) in department of medicine of Choithram Hospital and Research Centre, Indore. In the present study in all 30 diabetic hypertensives which were studied seven were females who constitute 23.33 % and 23 were males who constitute 76.67%. In the present study of the 30 participants mean CIMT of age group 40-50 years was found to be 0.70 ± 0.00, in age group 51-60 it was 0.83 ± 0.08, in age group 61-70 it was 0.83 ± 0.08, in age group more than 80 years it was 0.90 ± 0.00 respectively.

In 2008 a study was done Tim *et al.*; [24] which done on healthy population the mean CIMT in the present study is greater than that that found in the study done by Tim K *et al.*; this can be because the CIMT in diabetic hypertensives is more as compared to healthy subjects as showed in 2011 by Gómez-Marcos *et al.*; [25] who in their study did a concluded that the intima-media thickness was greater in diabetics, but the annual increase in the thickness was greater in hypertensive patients.

Hence it can be said the results of the present study with regards to CIMT are similar to that obtained in 2011 by Gómez-Marcos *et al.*; [25] Di Bello *et al.*; and Jarauta *et al.*; in 2010 [26].

In a study done by Jarauta *et al.*; [26] though the subjects were healthy, the results were astonishingly similar to the results of the present study i.e. in diabetic hypertensives in which CIMT is expected to be more. One explanation can be that the other risk factors for atherosclerosis which can lead to raised CIMT like smoking, metabolic syndrome, chronic kidney disease were not taken into account during selection of healthy subjects.

CRP

In the present study the mean CRP value was found to be 72.78 ± 36.43 mg/L (>6 mg/L is considered abnormal). Thus we can say the CRP value is significantly higher in the diabetic hypertensive group which has been studied. Shafi Dar *et al.*; [27] and did Mahajan *et al.*; [28] found similar results in their studies.

FIBRINOGEN

The mean fibrinogen level in the participants of the present study is 316.50 ± 104.60 (normal value 150 to 400) though it is the normal range it is on the higher side in the normal range Çoban *et al.*; [29] Kafle *et al.*; [30] Bembde *et al.*; [31] and Desai *et al.*; [32] in their studies found similar result as in the present study.

CRP AND IMT

The mean CIMT in all the participants is 0.81 ± 0.08 cm.

The mean CRP in total participants is 72.78 ± 36.43 mg/L.

A significant association was found between CRP and CIMT with a P value of 0.001. Kang *et al.*; [33] Kawamoto *et al.*; [34], Minoguchi *et al.*; [35], Elias-Smale *et al.*; [36], Baldassarre *et al.*; [37], and Debing *et al.*; [38], in their studies found results similar to the present study.

FIBRINOGEN AND IMT

The mean fibrinogen in total participants is 316.50 ± 104.60 mg/dL.

The mean C-IMT in all the participants is 0.81 ± 0.08 cm. A significant association was found between fibrinogen and CIMT with a p value of 0.033.

Sabeti *et al.*; [39], Baldassarre *et al.*; [37], Trappolini *et al.*; [40] and Green *et al.*; [41] in their studies found result similar to the present study.

From this study we can conclude that there is a significant association of markers of inflammation CRP and fibrinogen with carotid intimal thickness in diabetic hypertensives.

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