

Endothelial Dysfunction in Type IIIc Diabetes Mellitus and Chronic Pancreatitis

Nitin Jagtap, Hrushikesh Chaudhari, Jagadeesh Singh, Rupjyoti Talukdar, Pintu Bhakhar, Mohan Ramchandani, Manu Tandan, DN Reddy

Asian Institute of Gastroenterology, India

ABSTRACT

Aim and introduction Brachial artery flow mediated dilatation is an index of nitric oxide-dependent endothelial function that is impaired in patients with type 1 and 2 diabetes mellitus. We studied whether there is endothelial dysfunction in diabetes mellitus type IIIc and chronic pancreatitis as compared to normal. **Materials and methods** We analysed flow mediated dilatation in 31 patients with type IIIc diabetes mellitus (Group A), 34 patients with chronic pancreatitis only (Group B) and 33 age and sex matched controls (Group C) along with history of alcohol or smoking. We also studied flow mediated dilatation in respect to pancreatitis disease phenotype and diabetes mellitus status as evaluated by HbA1c. **Results** There was a statistically significant difference between groups as determined by oneway ANOVA ($F(2, 95) = 68.1$, p value 0.0001). A Tukey post hoc test revealed that the mean flow mediated dilatation was statistically significantly lower in group A (2.74 ± 1.28) compared to group B (4.39 ± 1.90) and group C (8.31 ± 2.51 , $p < 0.01$). There was statistical difference between group B and C ($p < 0.01$). Mean flow mediated dilatation was significantly lower in alcohol related chronic pancreatitis compared to idiopathic chronic pancreatitis ($2.04 \pm 0.68\%$ vs. $3.92 \pm 1.10\%$; $p < 0.05$) than controls who are smokers ($7.55 \pm 1.51\%$; p value 0.01). Mean flow mediated dilatation was significantly lower in alcohol related chronic pancreatitis ($3.15 \pm 1.43\%$) and idiopathic chronic pancreatitis ($4.35 \pm 1.83\%$) than controls who are not smokers ($8.88 \pm 2.97\%$; p value < 0.01). **Conclusion** Endothelial dysfunction as assessed by flow mediated dilatation was significantly impaired in chronic pancreatitis and type IIIc diabetes mellitus. Also, there was significant impairment in endothelial dysfunction in alcohol related chronic pancreatitis and those who continue to smoke.

INTRODUCTION

Brachial artery flow mediated dilatation (FMD) has been to be reduced in patient having endothelial dysfunction in cases of atherosclerosis, coronary artery disease and DM [1]. FMD evaluates the function of vascular endothelial cells, and reduced FMD is a predictive factor for major vascular complications including cardiovascular diseases [2]. Adults with type 1 and type 2 DM were reported to have decreased FMD [3, 4]. Interestingly, endothelial dysfunction may precede the development of DM. In this regard healthy non-diabetic subjects who have first degree relative with type II DM display impaired endothelium dependent vasodilatation as well as increased plasma markers of endothelial cell activation [5].

However, there are no studies which studied endothelial function in the form of FMD in type IIIc DM or chronic pancreatitis (CP). We aimed to study brachial artery flow mediated dilatation as a marker for endothelial dysfunction in patients with DM associated with chronic

pancreatitis and CP without DM, in comparison to normal controls. We also studied FMD in relation to etiology of pancreatitis either alcohol or idiopathic, history of smoking along with pancreatic disease phenotype and status of DM.

METHODS

After approval from Institutional review board, a total of ninety eight individuals were included in this prospective cross sectional observational study, after taking informed consent. All subjects in study were included from Medical Gastroenterology OPD at Asian Institute of Gastroenterology, Hyderabad.

A total of 143 patients were screened for study, out of which 45 patients were excluded. Consort diagram is depicted in **Figure 1**. Patients with acute exacerbation of chronic pancreatitis, infected fluid collections, active sepsis, hypertension, dyslipidaemia, coronary artery disease, pregnancy, post pancreatic surgery, pancreatic or extra pancreatic malignancy or severe co-morbidity including chronic liver disease were excluded from study. A total of ninety eight individuals were included in the study and divided into three groups. Group A included subjects with chronic pancreatitis with type IIIc DM; group B included subjects with chronic pancreatitis without IIIc DM; group C included subjects without CP or DM.

Chronic pancreatitis was diagnosed by presence of typical history of recurrent pancreatic pain and imaging evidence showing PD dilatation, PD stricture

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Correspondence Nitin Jagtap
Asian Institute of Gastroenterology
Medical Gastroenterology
India
Tel 09021727598
E-mail docnits13@gmail.com

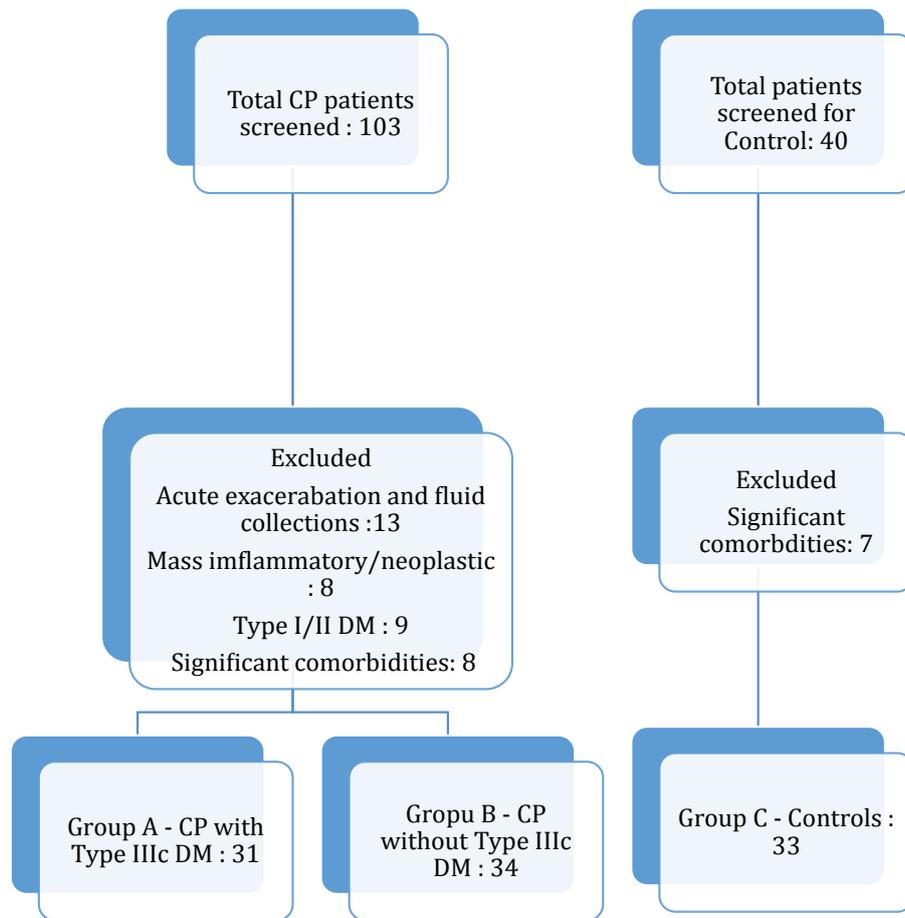


Figure 1. Consort diagram showing study and control population.

and calcification ductal and/or parenchymal. DM was diagnosed as per criteria proposed by ADA [6]. Type IIIc DM was differentiated from Type I and type II by clinical history and anti- GADD or c-peptide whenever necessary [7]. Demographic and clinical profile of enrolled patients was noted. All included patients were subdivided according aetiology of pancreatitis either alcohol related or idiopathic; also history of smoking was noted. Pancreatic disease phenotype was noted as exocrine, endocrine insufficiency, parenchymal or ductal calcification, and pancreatic ductal or common bile duct stricture and associated pancreas divisum. Pancreatic pain characteristics were noted as Izbicki’s score [8] and painDETECT [9]. Clinical and laboratory data of patient with DM was collected which included duration of diabetes mellitus, HbA1c. Controls were selected from Medical gastroenterology OPD who were diagnosed as functional bowel diseases, either acid peptic disease or irritable bowel syndrome with adequate matching for history of smoking and alcohol.

The brachial artery FMD assessment was performed once in all included patients using 7.5 MHz phased array linear transducer attached to HP Sonos 5500 echocardiography machine. Smoking was prohibited for at least four hours before test. The sphygmomanometer cuff was tied in the right arm with the patient in supine position. The brachial artery was imaged in the ante-cubital fossa and its diameter was measured. Brachial artery was then occluded with the sphygmomanometer

cuff inflation to at least 50mm Hg above systolic blood pressure for five minutes. Brachial artery diameter was measured again at one minute after deflation to assess FMD. FMD was calculated as percentage change in brachial artery diameter at 1 minute.

$$FMD = \frac{\text{Brachial artery diameter at 1min} - \text{Baseline diameter}}{\text{Baseline diameter}} \times 100$$

STATISTICAL ANALYSIS

The data for the present study was collected on pre-designed standard format. The data was entered in MS-excel after editing for completeness and consistency of the data. The values were expressed as mean and Standard deviation for continuous variables and as proportion for categorical variables. Student’s t test was applied for comparing the two groups for continuous variables. The chi-square, median or Fishers exact test was used for categorical variables in view of the small sample size. Spearman correlation coefficient analysis was used for continuous variables. Analysis of variance was used to compare multiple groups followed Tukey post hoc test. All reported P values are 2 tailed. A p value of 0.05 was regarded as statistically significant. The analysis was carried out using Statistical package for social Sciences (SPSS 20th version).

RESULTS

A total of 103 patients with chronic pancreatitis were screened for study population. Out of which 38

were excluded; 13 for acute exacerbation of CP or fluid collection, 8 for mass lesion in pancreas, 9 for either type I or type II DM and 8 for other significant comorbidities. 5 patients were diagnosed to have type I DM on basis of young age, history of ketoacidosis, low c-peptide levels (Mean 0.75 ng/ml) and Anti-GADD positivity. Four patients were diagnosed to have type II DM on basis of obesity, high c-peptide levels (Mean 3.8 ng/ml) and Anti- GADD negativity. These 9 patients were excluded as mentioned in **Figure 1**. To A total of 40 patients were screened for control group, out of which 7 were excluded due to presence significant comorbidities. A total of 98 were enrolled in the present study, which were divided into three groups. Group A (n=31) included patients with CP and type IIIc DM; group B (n=34) included patients with CP without diabetes; and group C (n=33) included patients without CP or DM. All subgroups were adequately matched for age, sex and history of smoking or alcohol intake. **Table 1** depicts demographic characteristics of study population. **Table 2** describes pancreatic disease phenotypes along with pain characteristics of group A and B.

There was a statistically significant difference between groups as determined by one- way ANOVA (F (2, 95) = 68.1, p value 0.0001) as depicted in **Figure 2**. A Tukey post hoc test revealed that the mean FMD was statistically significantly lower in group A (2.74±1.28) compared to group B (4.39±1.90) and group C (8.31±2.51, p<0.01). There was statistical difference between group B and C (p<0.01).

Subgroup analysis (**Figure 3**) revealed that mean FMD in the alcohol related CP (2.441±1.128) compared to idiopathic CP (4.324±1.802, p value 0.0055) and control (8.315±2.515, p value 0.0001). In alcohol related CP, there was no statistically difference of FMD between overall, smokers and non-smokers (p value >0.05). In idiopathic CP, there was no difference in mean FMD between overall, smokers and non-smokers (p value >0.05). In smokers, mean FMD of alcohol related CP (2.041±0.685) and idiopathic CP (3.92±1.095) was not statistically different (p value 0.9310), however significantly lower than controls who smoke (7.548±1.51, p value 0.0001). In non-smokers, mean FMD of alcohol related CP (3.153±1.43) and idiopathic CP (4.35±1.838) was not statistically different (p value 0.7626), however significantly lower than control who don't smoke (8.88±2.966, p 0.0001).

There was no significant difference in FMD as per presence of exocrine insufficiency, PD stricture, CBD stricture, parenchymal or ductal calcification (p value >0.05) by Chi-square test. There was no statistical correlation between PD size, Izbicki score and painDETECT (p value >0.05), however, there was statistically significant correlation between HbA1c and FMD (p value 0.005) using Spearman correlation coefficient analysis.

DISCUSSION

In the current study, we attempted to study endothelial dysfunction in the form of brachial artery FMD in patient

with chronic pancreatitis with or without type IIIc DM. We also evaluated pancreatic disease phenotype in the form of structural changes and pain scores (Izbicki score [8] and painDETECT [9]) and its relation with endothelial dysfunction.

To best of our knowledge, this is the first study which evaluated presence of endothelial dysfunction in type IIIc DM and CP. We used non-invasive, easy to perform and reproducible method to study endothelial dysfunction in the form of brachial artery reactivity. Brachial artery FMD is high – frequency ultrasonographic imaging of the brachial artery to assess endothelium dependent dilation of brachial artery following sheer stress [10]. The sheer stress provokes the release of nitric oxide, resulting in vasodilation the can be quantified and expressed as percentage as an index of endothelial function. Endothelium derived NO is principal mediator of FMD [11].

There is now adequate data exists to suggest that endothelial dysfunction occurs in both type I [12] and type II DM [13] as well as in insulin resistance without DM [5]. Also Ito H, et al in recent study found that The FMD was also lower in the subjects both with coronary artery disease (5.6±2.8%) and without coronary artery disease (6.1±3.3%) among the patients with diabetes compared to

Table 1. Baseline characteristics of study population.

Characteristics	Group A Type IIIc DM	Group B CP only	Group C Control	p value
Number	31	34	33	
Male/Female	26/5	27/7	25/8	0.79
Mean Age (± SD) years	40(± 11.8)	39(± 9.5)	38(±13.1)	0.72
Alcohol*	14(45.2)	11(32.4)	15(45.5)	0.46
Smoking*	13(41.9)	6(14.7)	14.4(42.4)	0.05
Mean duration of CP in months (±SD)	43.5(± 40.6)	41.3(± 39.5)	NA	

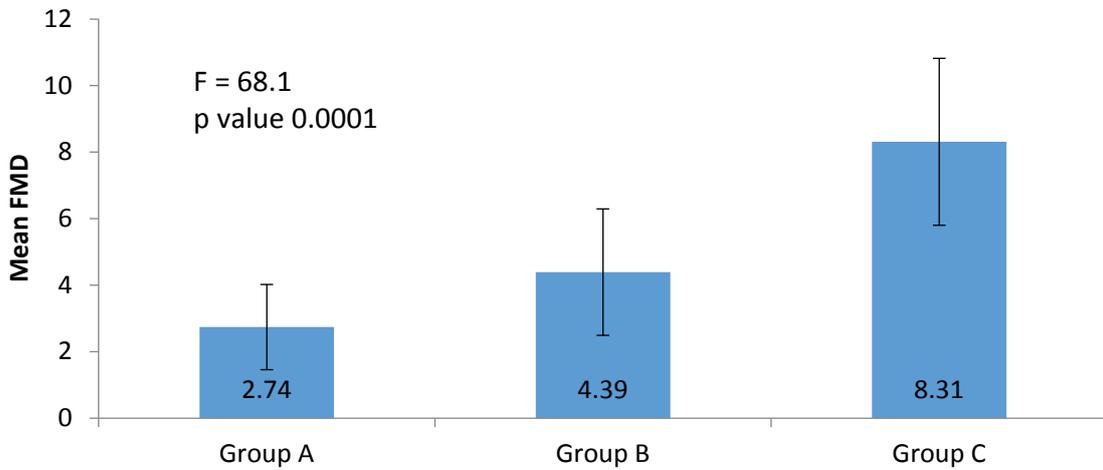
*Figures in parenthesis indicates percentage.

Table 2: Distribution of pancreatic disease phenotype.

	Group A	Group B	p value
Exocrine insufficiency*	11(35.9)	5(14.7)	0.08
Endocrine insufficiency*	31(100)	0	
Calcification*			
Parenchymal	18(58.1)	17(50)	0.69
Ductal	20(64.5)	12(35.3)	0.63
Stricture*			
PD	8(25.8)	12(35.3)	0.58
CBD	2(6.4)	5(14.7)	0.43
Pancreas divisum*	3(9.7)	6(17.7)	0.48
Pain characteristics			
Mean Izbicki score(SD)	30.5(±15.5)	34.4(±14.5)	
PainDETECT*			0.30
Nociceptive	17(54.8)	20(58.8)	
Unclear	9(29)	10(29.4)	0.87
Neuropathic	5(16.2)	4(11.8)	

* Figures in parenthesis indicates percentage.
CBD common bile duct; PD pancreatic duct

Comparison of mean FMD in pre-specified groups



Mean FMD in percentage as compared in Group A – IIIc DM, Group B – CP only and Group C – Controls

Figure 2. Comparison of mean FMD in pre-specified groups.

FMD analysis with respect to etiology and smoking

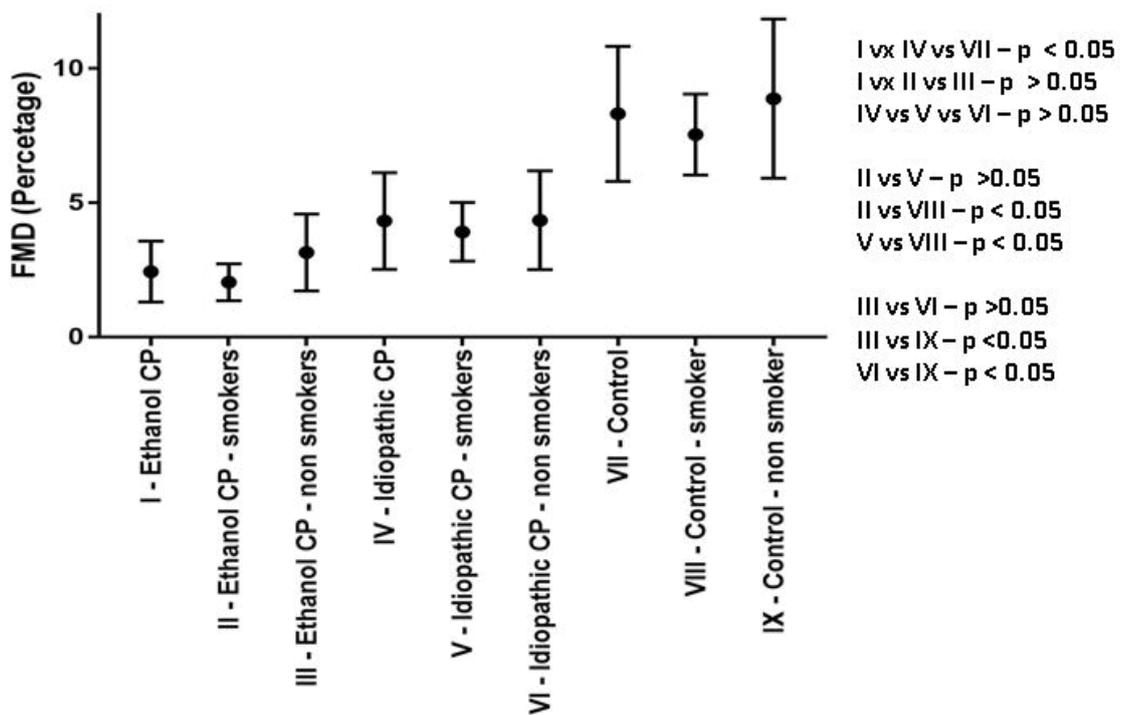


Figure 3. FMD analysis with respect to etiology and smoking.

those without both diabetes and CHD [14]. However, there are no studies in literature which evaluated endothelial dysfunction in type IIIc DM or CP. In our study we found that there is significant endothelial dysfunction in patient with type IIIc DM and CP. compared to controls. There was significant endothelial dysfunction in idiopathic CP compared to controls indicating that CP itself can have endothelial dysfunction, also there was significant endothelial dysfunction in alcohol related CP and idiopathic CP suggesting possible additional role of alcohol in promoting endothelial dysfunction. In patients with alcohol related or idiopathic CP, smoking may exacerbate

endothelial dysfunction. However due to small number of patient who smoke in idiopathic CP group it is difficult to interpret.

There was no difference in endothelial dysfunction according to diseases phenotype of CP. There was no correlation between PD size, Izbicki score and painDETECT, indicating that endothelial dysfunction in CP is not related to anatomical abnormalities and pain characteristics in the CP. However, there was linear correlation between HbA1c and FMD, indicating poor glycaemic control is related to more endothelial dysfunction, which is in concordance to previously published studies in type I and type II DM [15, 16].

Presence of endothelial dysfunction in CP and type IIIc DM may have role in progression of inflammation and fibrosis in chronic pancreatitis. Also presence of endothelial dysfunction in smokers and alcohol drinkers may be the factor responsible for faster progression of chronic pancreatitis in these patients. These findings need to be confirmed by larger studies and also it should be correlated with other markers of endothelium activation.

Conflicts of interests

The authors indicated no potential conflict of interests.

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