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Original Research Article

Intima-Media Thickness of Common Carotid Artery in Individuals with Impaired Fasting Glycemia in Comparison with Normal Healthy Adults by B-Mode Ultrasonography

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Abstract: Impaired fasting glucose is an important risk factor for subsequent development of both diabetes mellitus and cardiovascular diseases. One of the complications of diabetes is acceleration of atherosclerosis in blood vessels which leads to cerebro- and cardiovascular morbidity and mortality. The measurement of intima-media thickness (IMT) of common carotid artery (CCA) is highly reproducible and suitable non-invasive method to monitor early stages of atherosclerosis and it is considered an early surrogate marker of coronary atherosclerosis. Increased cardiovascular risk in individuals with impaired fasting glucose points towards an increased risk of atherosclerosis in these individuals as compared to those with normal glycemic values. The aim of this study is to compare the extent of carotid atherosclerosis as indicated by intima-media thickness of common carotid artery, between individuals with impaired fasting glycemia and normal healthy adults. The present study was a prospective comparative study carried out on 200 subjects, 100 cases with family history of type 2 diabetes mellitus and having impaired fasting glucose and 100 normal healthy controls without any family history of type 2 diabetes mellitus with normal fasting blood glucose. Overall, it was observed that obesity, dyslipidemia and systolic hypertension were more prevalent in cases than in healthy controls. The mean carotid intima-media thickness was also significantly higher in cases (0.728±0.089 mm) as compared to controls (0.636±0.068 mm) thus suggesting early and accelerated atherosclerosis in pre-diabetics. This study concluded that pre-diabetic individuals not only have elevated cardiovascular risk factors but also elevated levels of subclinical atherosclerosis, emphasizing the importance of dietary, lifestyle and/or pharmacologic interventions even before the onset of clinical diabetes.
Keywords: Impaired fasting glucose, intima-media thickness, atherosclerosis, diabetes mellitus, dyslipidemia

INTRODUCTION

Diabetes mellitus is the most common endocrine disorder around the globe. It comprises of a group of metabolic derangements that share the phenotype of hyperglycemia [1]. Both micro and macrovascular changes can occur in diabetes mellitus. The macrovascular complications like coronary artery disease, cerebrovascular disease and peripheral vascular disease are common causes of morbidity and mortality [2]. The natural history and pathogenesis of diabetes indicate that this disease has a prolonged prediabetic phase. Patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) are at significant risk for diabetes mellitus [3] and thus are an important target group for primary prevention. Impaired glucose tolerance is defined as two-hour glucose levels of 140 to 199 mg per dL (7.8 to 11.0 mmol) on the 75-g oral glucose tolerance test, and impaired fasting glucose is defined as glucose levels of 100 to 125 mg per dL (5.6 to 6.9 mmol per L) in fasting patients. These glucose levels are above normal but below the level that is diagnostic for diabetes. The natural history of both IFG and IGT is variable, with 25% progressing to diabetes,

50% remaining in their abnormal glycemic state, and 25% reverting to normo glycemia [4, 5].

One of the complications of diabetes is acceleration of atherosclerosis in blood vessels. The atherosclerotic lesions tend to be local and ischaemia caused by atherosclerosis is one of the major causes of disease and death [6]. It has been demonstrated that both IFG and IGT are risk factors for the subsequent development of cardiovascular disease [7, 8]. Increased knowledge of mechanisms involved in the gradual development of atherosclerosis point towards an increased risk of atherosclerosis in prediabetic individuals in comparison to those with normal glycemic values [9].

The key process in atherosclerosis is intimal thickening and lipid accumulation. An atheromatous plaque consists of raised focal region initiating within the intima having a soft yellow grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a firm white fibrinous cap. Atherosclerotic lesions usually involve only a partial circumference of the arterial wall (eccentric lesion) [8].

The carotids provide a convenient window for the assessment of the whole vascular system. Pattern of development of atheroma vary for different arterial areas. However, it could be expected that changes in the carotids might be related to disease in other vessels such as the coronary arteries, and that changes in the carotids might allow some prediction of severity of this disease [10]. Over the past two decades, carotid sonography has largely replaced angiography as the principal screening examination to assess suspected extra cranial carotid atherosclerotic disease. Gray scale, colour Doppler, power Doppler and pulsed Doppler imaging techniques are routinely employed in the evaluation of patients with neurologic symptoms and suspected extra cranial carotid vascular disease. Besides, ultrasound is an inexpensive, non-invasive and highly accurate method of diagnosing carotid stenosis, which is why reliance on carotid sonography without preoperative angiography is becoming increasingly common [9]. The intima-media thickness (IMT) of the carotid artery is best demonstrated in the upper common carotid artery where the vessel is usually at right angles to the ultrasound beams. Longitudinal views of the layers of the normal carotid wall demonstrate two nearly parallel echogenic lines, separated by a hypoechoic to anechoic region. The first echo, bordering the vessels lumen represents the lumen intimal interface; the second echo is caused by the media adventitia interface. The media is the anechoic/hypoechoic zone between the echogenic lines. The distance between these lines represents the combined thickness of the intima and media complex (IM complex) [9]. With careful attention to detail, it is possible to measure IMT with satisfactory, reproducible accuracy. The precise upper limit of the normal range is a matter of some discussion. It does increase with age but values of less than 0.8 mm correlate well with lack of coronary artery disease, whereas an increasing thickness above this level is associated with increasingly severe coronary artery disease and an increased risk of myocardial infarction.

In the present study, we have compared the carotid atherosclerosis as indicated by IMT measured by B mode ultrasonography in individuals with impaired fasting glycemia and normal healthy adults, both belonging to the same age group (18-45 years).

MATERIAL AND METHODS

This was a prospective comparative study conducted in the department of Medicine and Radiology of a tertiary care teaching hospital of Punjab, India. A total of 200 subjects were included and they were divided into 2 groups. Group A included 100 cases with family history of type 2 diabetes mellitus and having impaired fasting glycemia i.e. Fasting blood glucose (FBG) of 100-125 mg/dl in accordance with the American Diabetes Association (ADA) guidelines. Group B included 100 normal healthy controls without any family history of type 2 diabetes mellitus with normal FBG (<100 mg/dl). All subjects were in the age group of 18-45 years. These subjects were recruited from the Medicine outdoor and indoor departments and written informed consent was taken from each participant before enrolling him/her for the study. The data was collected by the first author as per the detailed questionnaire. Patients having type 1 or type 2 diabetes mellitus, any endocrine disorder, cirrhosis or any other significant illness, having any evidence of arteritis or connective tissue disorders, those already operated for carotid stenosis or on treatment with antihypertensives, antiobesity and hypolipidemic drugs were excluded from the study.

Detailed history including the family history of diabetes was taken. Thorough general and physical examination including measurement of body mass index (BMI), waist and hip circumference were done. After an overnight fast, plasma glucose, lipid profile, haemogram, liver function and renal function tests were performed.

Carotid ultrasonic examination was performed with the patient supine, neck slightly extended and the head turned away from the side being examined. The intima-

media thickness (IMT) of the carotid arteries was determined by using a high resolution B mode ultrasonography system ENVISOR (Phillips) version B.O.-I having an electrical linear transducer mid frequency of 7.5 MHz. Scanning was done for 20 minutes. Scans were obtained along the entire course of the cervical carotid artery, from the supraclavicular notch cephalad to the angle of mandible. The IMT was defined as the distance from the leading edge of first echogenic line to the second echogenic line. The first echogenic line represented the lumen intimal interface and second line was produced by the collagen containing upper layer of the intimal adventitia. At each longitudinal projection, determination of the IMT was conducted at the site of greatest thickness and two points 1 cm upstream and 1 cm downstream from the site of greatest thickness. Total 6 IMT measurements were taken 3 on left side and 3 on right side. Their mean was taken as representative value for each subject.

OBSERVATION

Subjects aged between 18-45 years were divided into two groups, group A included cases with impaired fasting glucose (IFG) with positive family history of diabetes mellitus (FH^{+ve}) and group B included normal healthy individuals having normal fasting glucose (NFG) without any family history of diabetes mellitus (FH^{-ve}). Both the groups were age and sex matched in distribution. The mean age of group A (IFG) was 31.45±3.95 years and mean age of group B (NFG) was 31.50±7.680 years. It was observed that mean weight and mean BMI of group A (IFG) subjects were higher (72.52±11.19 kgs and 27.01±3.85 respectively) than group B (NFG) (64.15±7.81 kgs and 23.89±0.92 respectively). The differences in these parameters between the two study groups were statistically highly significant. Mean waist to hip ratio of group A (IFG) was 0.931±0.040 and that of group B (NFG) was 0.912±0.016 and the difference observed thereof was also statistically highly significant.

Mean systolic blood pressure in group A (IFG) was 127.10±6.29 mm Hg and that in group B (NFG) was 121.46±9.13 mm Hg. The p value was <0.001 which was statistically highly significant. Mean diastolic blood pressure in group A (IFG) was 78.74±5.41 mm Hg and that in group B (NFG) was 77.26±6.11 mm Hg. The p value was 0.071 which was statistically insignificant. Mean fasting glucose of group A (IFG) was 109.55±7.90 mg/dl and that of group B (NFG) was 82.11±4.60, with statistically significant p value.

Mean HDL level in group A (IFG) was 44.45±4.5 mg%, while it was 51.34±3.65 mg% in group B (NFG). The p value was <0.001 which was statistically highly significant. Mean serum triglyceride, total cholesterol and LDL levels were higher in group A (IFG) (152.20±36.60 mg%, 187.36±22.86 mg% and112.12±19.10 mg% respectively) as compared to group B (NFG) (118.58±36.13 mg%, 168.89±20.48 mg%, 93.61±16.88 mg% respectively), and the differences in these parameters between the two groups were statistically highly significant (Table 1, Figure 1).

Table 1: Lipid profile in the two study groups

Study Groups	Mean HDL (mg/dl)	Mean Triglyceride (mg/dl)	Mean Total Cholesterol (mg/dl)	Mean LDL (mg/dl)
Group A IFG (FH^{+ve})	44.45±4.50	152.2±36.60	187.36±22.86	112.12±19.10
Group B NFG (FH-^{ve})	51.34±3.65	118.58±36.13	168.89±20.48	93.61±16.88

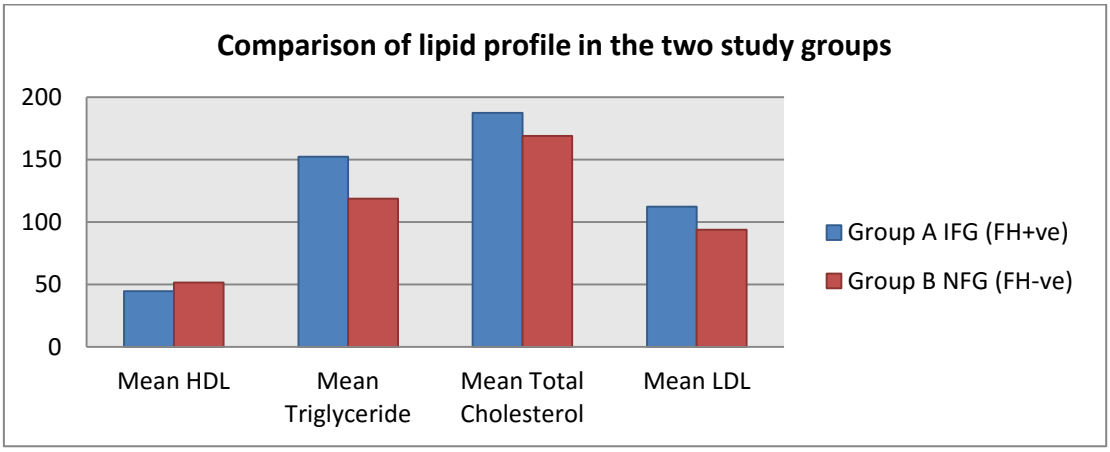

Fig 1: Comparison of lipid profile in the two study groups

Mean carotid IMT in group A (IFG) was 0.728±0.089 mm while the same in group B (NFG) was 0.636±0.068. The t value was 8.16 and p value was <0.001 which was statistically highly significant (Table 2, Figure 2).

Table 2: IMT OF CCA (in mm) in the two study groups

Group	Mean IMT (mm)	SD
Group A IFG (FH^{+ve})	0.728	0.089
Group B NFG (FH^{-ve})	0.636	0.068

t – Value 8.16

p – Value <0.001 ^{HS}

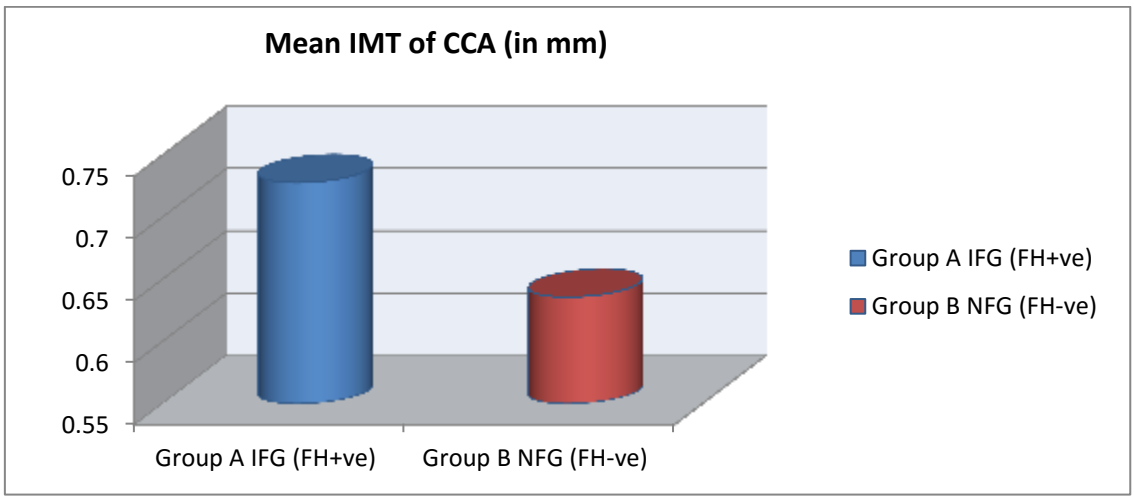

Fig 2: Comparison of mean IMT of CCA (in mm) in the two study groups

DISCUSSION

The intima-media thickness (IMT) of common carotid artery (CCA) is considered to be an excellent non-invasive measure of generalized atherosclerosis. It is extensively used to examine the stage of atherosclerosis and to evaluate the regression of atherosclerotic lesions with intervention therapies. It has been suggested that aorta, carotid and cerebral arteries undergo atherosclerotic process at the same age as the coronary arteries. Moreover there is good agreement between histological examination and the ultrasonographic evaluation of carotid artery atherosclerosis.

Earlier studies have reported ethnic differences in morbidity and mortality due to coronary artery disease

and similar ethnic differences were observed in carotid IMT too. These differences emphasized the need for study in different population groups. The present study presents data on carotid IMT in North Indian Punjabi population.

In the present study, mean carotid IMT was more in individuals with impaired fasting glucose (IFG) (0.728±0.089 mm) as compared to individuals with normal fasting glucose (NFG) (0.636±0.068 mm). This difference was statistically highly significant ($p<0.001$). Though the mean value of IMT of CCA in individuals with IFG with positive family history of diabetes was less than 0.8 mm, which is considered a marker of increased cerebro- and cardiovascular disease, however, the difference in the mean values of carotid IMT in the two study groups was statistically highly significant. Thus, the present study provides direct evidence at the vascular level that atherosclerotic process begins well before the clinical onset of diabetes in individuals with IFG having positive family history of diabetes mellitus. Kao *et al.;* [11], in a similar study also observed a significant correlation between family history score and increased CCA IMT (0.006 mm increase in CCA IMT for every point increase of family history score) than in persons with no history of diabetes mellitus. Makimattila *et al.;* [12] also showed that positive family histories of type II diabetes and hypertension are independent predictors of increased carotid IMT in patients, and could therefore predispose these patients to atherosclerosis. Similar results were also demonstrated by studies done by Panacciulli *et al.;* [13], and Faeh *et al.;* [14]. Hunt *et al.;* [15] in their study reported that both cardiovascular disease risk and CCA IMT were elevated in individuals before the clinical onset of diabetes. This study reported that the mean IMT of CCA was 0.72 mm in prediabetic individuals in comparison with nondiabetic individuals who had a mean value of 0.69 mm.

In the present study, it was observed that mean values of BMI and systolic blood pressure were higher in individuals with IFG and positive family history of diabetes in comparison to control subjects. Hunt *et al.;* [15] also observed that in comparison to nondiabetic individuals, pre-diabetics of similar age groups had a higher BMI ($p<0.05$) along with increased systolic blood pressure. Another study by Kao *et al.;* [11] revealed that BMI ($p=0.002$) and systolic blood pressure ($p=0.021$) were independent determinants of increased carotid IMT in individuals with positive family history of diabetes. Makimattila *et al.;* [12] also showed that increased BMI and higher mean arterial blood pressure in individuals with positive family history of diabetes mellitus were associated with increased IMT of CCA.

In the present study high serum triglycerides and low HDL levels were seen in individuals with IFG (FH+ve) in comparison with NFG (FH-ve) individuals, which were statistically highly significant favoring the theory that atherosclerosis begins to occur much earlier than the clinical onset of overt diabetes in patients with IFG (FH+ve). Panacciulli *et al.;* [13], in their study also observed independent association of IMT of CCA with low HDL concentration ($p<0.001$) and with high serum triglyceride levels ($p<0.01$). Hunt *et al.;* [15] also observed that IMT of CCA was more in pre-diabetic subjects who had high serum triglycerides and low HDL levels in comparison with normal individuals.

The present study also showed that IFG (FH+ve) individuals had higher mean LDL levels in comparison to NFG (FH-ve) individuals, which may have contributed to increased atherosclerosis resulting in increased IMT of CCA in the former group. Hunt *et al.;* [15] and Faeh *et al.;* [14] also observed that subjects with high LDL had an increased carotid IMT. In another study by Makimattila *et al.;* [12], high serum LDL cholesterol was associated with increased carotid IMT, which was statistically significant.

In the present study, increased serum cholesterol levels were observed in individuals with IFG (FH+ve) which could contribute to accelerated atherosclerosis and thus greater CCA IMT. Kao *et al.;* [11] also showed that IFG individuals had significant higher total serum cholesterol levels and greater IMT.

Thus the present study showed early onset of atherosclerosis as demonstrated by increase in carotid IMT in individuals with IFG and positive family history of diabetes mellitus as compared to individuals with NFG and negative family history of diabetes. High BMI, increased levels of LDL, total serum cholesterol and serum triglycerides, and low levels of HDL are observed in pre-diabetics which serve as independent risk factors for early atherosclerosis and increased cardiovascular risk in these individuals even before the onset of frank diabetes mellitus.

CONCLUSIONS

- Impaired fasting glucose with positive family history of diabetes mellitus is an important risk factor for development of atherosclerosis as observed by increase in the intimal medial thickness of common carotid artery.

- Increased carotid intimal medial thickness in individuals with impaired fasting glucose and positive family history of diabetes mellitus provides direct evidence at the vascular level that atherosclerosis begins well before the clinical onset of diabetes mellitus.
- Obesity, as shown by increased BMI and increased waist-hip ratio, is more prevalent in individuals having impaired fasting glucose with positive family history of diabetes mellitus.
- Dyslipidemia, in the form of higher levels of serum triglycerides, serum LDL, serum cholesterol, and lower levels of serum HDL, is common in individuals having impaired fasting glucose with positive family history of diabetes mellitus.
- Higher systolic blood pressure is encountered in individuals having impaired fasting glucose with positive family history of diabetes mellitus.
- Obesity, dyslipidemia and systolic hypertension are independent risk factors of atherosclerosis and their presence in pre-diabetic individuals contribute significantly to accelerated atherosclerosis in these individuals and lead to potential cardiovascular risk even before the onset of frank diabetes mellitus.

Thus, the present study concludes that prediabetic individuals not only have elevated cardiovascular risk factors but also elevated levels of subclinical atherosclerosis, emphasizing the importance of dietary, lifestyle and/or pharmacologic interventions even before the onset of clinical diabetes.

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