Carotid intima-media thickness as a predictor of atherosclerosis in diabetic and non-diabetic subjects - A study from tertiary care hospital in coastal city of South India

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ABSTRACT

Background and Objectives: Atherosclerosis typically occurs over a period of many years, usually many decades. After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. Evaluation of intimal medial thickness is considered as surrogate marker of atherosclerosis. B-mode ultrasound was a suitable non-invasive method to visualize the arterial walls and to monitor the early stages of the atherosclerotic process.

Materials and Methods: This is a cross-sectional hospital-based study. A total of 100 patients were selected with 50 patients each in diabetic and non-diabetic groups. After taking consent, patients were subjected for carotid Doppler examination.

Results: The mean intimal medial thickness values of the diabetic subjects (0.12) were significantly higher than those of the non-diabetic (0.07 mm) subjects ($P < 0.001$). Both in the normal and diabetic subjects, these values increased with age. At any given age, the diabetic subjects had higher values than the non-diabetic subjects. Intimal medial thickness showed a positive correlation with age, gender, hypertension (HTN), hemoglobin A1C, and duration of diabetes with statistically significant P value.

Conclusion: Diabetic subjects have higher intimal medial thickness values than non-diabetic subjects. Diabetes, duration of diabetes, age, gender, and HTN are the most important risk factors associated with increased intimal medial thickness.

Key words: Atherosclerosis, carotid intima-media thickness, ultrasound

INTRODUCTION

Sonographic evaluation of the carotid artery intima-media thickness is a simple, non-invasive, and reproducible imaging parameter to evaluate atherosclerosis and atherosclerotic vascular diseases.

Recently, considerable attention has been directed at the wall thickness of the carotid arteries as an early marker of atherosclerotic disease and as a means of showing the effectiveness of medical therapies in treating atherosclerosis. Non-invasive techniques such as B-mode ultrasound (USG) can directly assess the intima-media thickness (IMT), which corresponds to the thickness of the histologic intima and media.[1-3]

USG imaging of carotid vessels can provide information on carotid intima-media thickness (CIMT), plaque presence and type, calcification, and wall diameter, offers the ability to examine pre-symptomatic lesions, and assess atherosclerotic burden, and hence, the risk of cardiovascular and cerebrovascular events.

Such non-invasive screening procedures are valuable in identifying diabetic patients at risk for coronary artery disease

(CAD) and cerebrovascular disease. In clinical settings, this can potentially lead to early interventions.

The carotid arteries are among the vessels that are prone to developing overt atherosclerotic lesions in the presence of risk factors such as cigarette smoking, hypertension (HTN), diabetes, and dyslipidemia.[4,5]

Patients with diabetes mellitus (DM) suffer unduly from premature and severe atherosclerosis. The Framingham study pointed out that diabetic individuals have higher serum concentrations of lipids and more HTN, obesity, and thus are more prone to metabolic syndrome and its sequelae, namely, CAD, cerebrovascular disease, and vascular atherosclerosis.[6]

In type 2 DM, carotid intimal thickness is significantly higher than in corresponding healthy age- and sex-matched non-diabetic subjects. There is also evidence for an excess prevalence of intimal thickening and atherosclerotic lesions in patients suffering from definite HTN compared with normotensive controls.[7-9]

Hence, measurement of carotid intimal thickness using high-resolution B-mode ultrasonography which is non-invasive

well-validated method is used to assess early manifestations of atherosclerosis such as early cardiovascular disease, T1A, stroke in symptomatic, as well as high-risk patients such as dyslipidemia, DM, HTN, and cigarette smoking.

Aims and Objectives
- To measure CIMT in subjects with and without DM.
- Correlation of CIMT with risk factors such as age, HTN, smoking, and dyslipidemia.

MATERIALS AND METHODS

This study is a comparative study of 50 cases and 50 controls in which we have studied the CIMT values in diabetic and non-diabetics.

Method of Collection of Data
Inclusion criteria
- Patients aged more than 30 years with type2 DM.
- Patients with HTN.

Exclusion criteria
- Patients with ischemic heart disease (acute coronary syndrome, stable angina, prior history of coronary artery bypass graft, and percutaneous coronary angioplasty).
- Patients with congestive heart failure.
- Patients with renal disease both acute and chronic.
- Patients with stroke.
- Patients with type 1 DM.

Statistics
The data obtained from the above was filled in the master chart and analyzed further for their statistical significance. Data were presented as mean ± SD values were called statistically significant (if $P < 0.05$). The correlation coefficient test and Student's t-test was used in most cases to compare frequency distribution.

RESULTS

In age group 40–50 years, there are 10 cases and 11 controls.

In age group 51–60 years, there are 13 cases and 12 controls.

In age group 61–70 years, there are 27 cases and 27 controls which correspond to 54% [Table 1].

In age group 40–50 years, CIMT in cases is 0.08 ± 0.03, in controls, it is 0.07 ± 0.01.

In age group 51–60 years, CIMT in cases is 0.11 ± 0.04, in controls, it is 0.074 ± 0.01.

In age group 61–70 years, CIMT in cases is 0.13 ± 0.021, in controls, it is 0.07 ± 0.02

Mean CIMT (0.13 ± 0.021) is more in the age group of 61–70 years, as age increases, CIMT also increased in cases [Table 2].

In cases, 74% (n = 37) are males and 26% (n = 13) are females.

In controls, 74% (n = 37) are males and 26% (n = 13) are females [Table 3].

In cases, mean CIMT in males is 0.097 ± 0.04 and in females 0.17 ± 0.030.

In controls, mean CIMT in males is 0.07 ± 0.02 and in females 0.07 ± 0.024 [Table 4].

CIMT between 0.01 and 0.05 cm group, there are 4 cases and 5 controls.

CIMT between 0.06 and 0.10 cm group, there are 28 cases and 42 controls.

CIMT between 0.11 and 0.15 cm group, there are 14 cases and 3 controls.

CIMT between 0.16 and 0.20 cm group, there are 4 cases.

Of 50 cases, 46 patients had CIMT between 0.06 and 0.20 cm (92%), and of 50 controls, 45 had CIMT between 0.06 and 0.20 cm (90%).

Mean CIMT in cases is 0.121 ± 0.015 cm, and in controls, it is 0.07 ± 0.02 cm [Table 5].

Patients with above the normal values in the profile were defined as risk group and patients with normal and below normal values were defined as non-risk group normal total cholesterol (TC)

Table 1: Age distribution of patients studied

Age in years	Cases n (%)	Controls n (%)
40–50	10 (20.0)	11 (22.0)
51–60	13 (26.0)	12 (24.0)
61–70	27 (54.0)	27 (54.0)
Total	50 (100.0)	50 (100.0)
Mean±SD	60.62±8.66	60.42±8.35

SD: Standard deviation

Table 2: Comparison of CIMT in two groups studied according to age in years

Age in years	Cases	Controls	P
40–50	0.08±0.03	0.07±0.01	0.151
51–60	0.11±0.04	0.074±0.01	0.014*
61–70	0.13±0.021	0.07±0.02	0.105

CIMT: Carotid intima-media thickness

Table 3: Gender distribution of patients studied

Age in years	Cases	Controls
	n (%)	n (%)
Male	37 (74.0)	37 (74.0)
Female	13 (26.0)	13 (26.0)
Total	50 (100.0)	50 (100.0)

Table 4: Comparison of CIMT in two groups studied according to gender

Gender	Cases	Controls	P
Male	0.097±0.04	0.070±0.02	<0.001**
Female	0.17±0.030	0.07±0.024	0.217

CIMT: Carotid intima-media thickness

value ≤200, triglyceride (TG) value ≤150, high-density lipoprotein value ≤40, low-density lipoprotein (LDL) value ≤100, very LDL value ≤30 [Tables 6-9].

Table 5: Comparison of average CIMT in two groups studied

CIMT	Cases	Controls
	n (%)	n (%)
0.01–0.05	4 (8.0)	5 (10.0)
0.06–0.10	28 (56.0)	42 (84.0)
0.11–0.15	14 (28.0)	3 (6.0)
0.16–0.20	4 (8.0)	0 (0.0)
Total	50 (100.0)	50 (100.0)
Mean±SD	0.121±0.015	00.07±0.002
Inference	Mean CIMT is significantly more in cases when compared to controls with P=0.035*	

CIMT: Carotid intima-media thickness, SD: Standard deviation

Table 6: Distribution of blood sugar parameters in two groups of patients studied

CIMT	Cases	Controls	P
	n (%)	n (%)	
FBS mg/dl			
<110	0 (0.0)	39 (78.0)	<0.001**
110–140	9 (18.0)	11 (22.0)	
>140	41 (82.0)	0 (0.0)	
PPBS mg/dl			
<140	0 (0.0)	24 (48.0)	<0.001**
140–200	0 (0.0)	26 (52.0)	
>200	50 (100.0)	0 (0.0)	

CIMT: Carotid intima-media thickness

Table 7: Effect of FBS/PPBS on CIMT

Parameter	Risk	Mean CIMT	Non-risk	Mean CIMT
FBS	n=50	0.054±0.03	n=50	0.061±0.04
PPBS	n=50	0.054±0.03	n=50	0.061±0.04

P=0.698. CIMT: Carotid intima-media thickness

Table 8: Distribution of serum lipid profile parameters in two groups of patients studied

Lipid parameters	Cases	Controls	P
	n (%)	n (%)	
TC mg/dl			
<200	18 (36.0)	39 (78.0)	<0.001**
>200	32 (64.0)	11 (22.0)	
LDL mg/dl			
<130	27 (54.0)	40 (80.0)	<0.001**
>130	23 (46.0)	10 (20.0)	
TG mg/dl			
<150	1 (2.0)	27 (54.0)	<0.001**
>150	49 (98.0)	23 (46.0)	
HDL mg/dl			
<40	34 (64.0)	13 (26.0)	<0.001**
>40	16 (32.0)	37 (74.0)	

TG: Triglyceride, HDL: High-density lipoprotein, TC: Total cholesterol

Mean CIMT value 1.30 ± 0.23 is highest between 7 and 10 years duration. There is incremental increase in CIMT value as the duration of DM progress. Statistical significance was achieved when the duration of DM was compared with CIMT value.

Risk group and non-risk group has been categorized depending on hemoglobin A1C (HbA1C) level >7 and <7, respectively. Mean CIMT in risk group of DM subjects is higher than the non-risk group, but P = 0.0004 highly statistically significant [Graph 1 and Table 10].

There were 15 and 14 patients in risk and non-risk group with CIMT <0.08 and 5 and 16 patients among risk and non-risk group with CIMT >0.08. P = 0.04 which is statistically significant [Table 11].

The mean CIMT in BMI <23 is 0.046 and BMI >23 mean CIMT is 0.072, P = 0.006 [Graph 2 and Table 12].

The mean CIMT in the study group is more in patients with DM+HTN+SMOKING (0.16 ± 0.25) compared to other patients [Table 13].

The mean CIMT in control group is relatively more in patients with HTN+SMOKING (0.08 ± 0.001) group compared to other group [Table 14].

The mean CIMT is increased in DM+HTN+SMOKING group (0.16 ± 0.25) which indicates risk factors contributes to the development of atherosclerosis [Table 15].
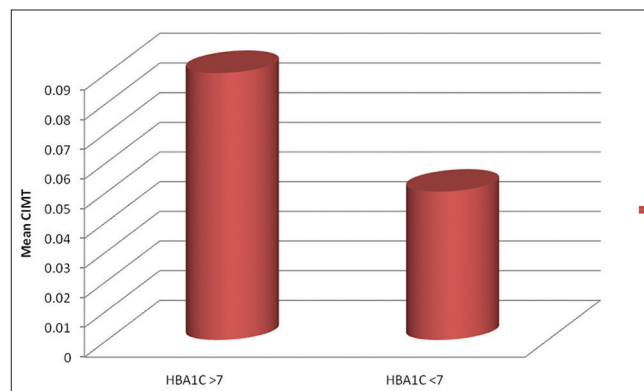
Graph 1: Effect of hemoglobin A1C on CIMT among diabetes mellitus
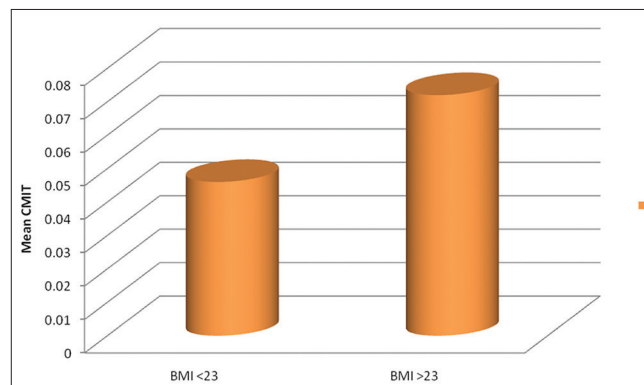
Graph 2: Effect of body mass index on carotid intima-media thickness

Table 9: Effect of lipid profile on CIMT

Parameter	Risk group		Non-risk group		Mean difference	P
	Mean CIMT	SD	Mean CIMT	SD		
TC	1.2229	0.3647	1.1389	0.04485	0.0840	0.59 (NS)
TG	1.2433	0.3412	1.1926	0.3958	0.0507	0.83 (NS)
HDL	1.2592	0.4069	1.1567	0.3771	0.1025	0.48 (NS)
LDL	1.2110	0.3819	1.1910	0.3973	0.0200	0.89 (NS)

CIMT: Carotid intima-media thickness, TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NS: Not significant

Table 10: Effect of duration of diabetes on CIMT

DM	Duration (years)	No	Mean CIMT
1	1–3	20	0.77±0.19
2	4–6	15	0.88±0.13
3	7–10	15	1.30±0.23

ANOVA, F=18.82, $P<0.001$ HS. CIMT: Carotid intima-media thickness, HS: Highly significant, DM: Diabetes mellitus

Table 11: Effect of HTN on CIMT

Parameter	<0.08	>0.08	Total
Risk	15	5	20
Non-risk	14	16	30
Total	29	21	50

$P=0.04$. CIMT: Carotid intima-media thickness, HTN: Hypertension

Table 12: Effect of smoking on CIMT

Parameter	<0.08	>0.08	Total
Risk	20	12	32
Non-risk	9	9	18
Total	29	21	50

$P=0.39$. CIMT: Carotid intima-media thickness

DISCUSSION

Effect of Age on CIMT

In the present study, cases and controls in the age groups of 40–50, 51–60, and 61–70 years, mean age being 60 years and more number of patients are in the age group of 61–70 years (27 cases). As the age increases, mean CIMT in cases has increased compared to controls that is mean CIMT in cases in the age group of 41–50 years is 0.08 cm, 51–60 years is 0.11 cm, and 61–70 years is 0.13 cm. In cases, mean CIMT is 0.121 cm (range 0.04–0.019 cm), and in controls, mean CIMT is 0.07 cm (range 0.04–0.15 cm).

Sahoo et al.,[4] Salonen et al.,[10] Howard et al.,[12] and Allan et al.[11] showed a positive correlation between age and CIMT [Table 16]

Effect of Gender on CIMT

In this study, there are 37 males and 13 females in both cases and control groups, in cases, mean CIMT in males is 0.097 ± 0.04 cm and in females is 0.17 ± 0.03 cm. In controls, mean CIMT is 0.07 ± 0.02 cm in both males and females. Mean CIMT is more in female cases than males, but female cases are less in number in our study. Mean CIMT is significantly more in male cases when compared to male controls with $P < 0.0001$.

The present study correlates with the study conducted by Sahoo et al. showed differences in mean CIMT between males and females in cases were not significant; however, the difference was statistically significant in both the genders when compared to controls with $P < 0.001$ [Table 17].

Comparison of CIMT among Diabetic and Non-diabetics

In this study, in cases, mean CIMT is 0.121 cm (range 0.04–0.19 cm), and in controls, mean CIMT is 0.07 cm (range 0.04–0.15 cm). Mean CIMT is significantly more in cases when compared to controls with $P = 0.0001$.

This study is correlating with the study conducted by Sahoo et al., mean CIMT in cases was 0.0782 cm (range 0.05–0.15 cm), and in controls, it was 0.059 cm (range 0.04–0.09 cm) with $P<0.0001$, and also with the study conducted by Mohan et al. ($P = 0.0001$) [Table 18].

Effect of HTN on CIMT

In this study, mean CIMT of hypertensive and non-hypertensive patients in study group was 0.12 ± 0.25 and 0.09 ± 0.03. Mean CIMT of hypertensive and non-hypertensive patients in control group was 0.08 ± 0.02 and 0.06 ± 0.01 ($P = 0.04$). This study is correlating with the study by O'Leary et al. ($P = 0.01$) and Agarwal et al. ($P = 0.05$) [Table 19].

Effect of Smoking on CIMT

In this study, 10% of study group are smokers with mean CIMT of 0.09 ± 0.04 and non-smokers with mean CIMT of 0.08 ± 0.04 ($P = 0.63$). In control group, mean CIMT of smokers 0.06 ± 0.01 and non-smokers 0.06 ± 0.01 ($P = 1.0$). In this study, there was no significant difference in CIMT between smokers and non-smokers. Due to less number of patients and duration of smoking was not considered in this study, hence, this study failed to achieve statistical significance on the effect of smoking on CIMT.

Effect of Lipid Profile on CIMT

In this study, various parameters of lipid profile have shown a positive correlation with CIMT in study group though a statistical difference could not be assumed between risk and non-risk group due to the less sample size.

Effect of FBS and PPBS on CIMT

Role of FBS-PPBS as an influencing factor on CIMT is doubtful, due to the selection of random samples.

In this study failed to assume the significant difference between risk and non-risk group due to the selection of random value.

Table 13: Comparison of CIMT in DM with or without HTN and smoking

DM±HTN (N)	Mean CIMT	DM without HTN	Mean CIMT	DM±HTN±smoking	Mean CIMT
18	0.12±0.25	13	0.09±0.03	12	0.16±0.25

CIMT: Carotid intima-media thickness, HTN: Hypertension, DM: Diabetes mellitus

Table 14: Comparison of CIMT in non-diabetic with or without HTN and smoking

Non-DM with HTN	Mean CIMT	Non-DM without HTN	Mean CIMT	Non-DM±smoking	Mean CIMT	Non-DM±HTN±smoking	Mean CIMT
16	0.08±0.02	17	0.06±0.01	8	0.06±0.01	11	0.08±0.01

CIMT: Carotid intima-media thickness, HTN: Hypertension

Table 15: Comparison of CIMT in both diabetic and non-diabetic with risk factors

No	DM±HTN	DM±smoking	DM±HTN±smoking	Non-DM±HTN	Non-DM±smoking	Non-DM±HTN±smoking
Mean CIMT	0.12±0.25	0.08±0.04	0.16±0.25	0.08±0.02	0.06±0.01	0.08±0.01

CIMT: Carotid intima-media thickness, HTN: Hypertension, DM: Diabetes mellitus

Table 16: Showing effect of age on CIMT I various studies

Study	Sahoo et al.[4]	Salonen et al.[12]	Allan et al.[16]	Howard et al.[11]	Present study
P	<0.05	0.04	0.05	0.05	0.014

CIMT: Carotid intima-media thickness

Table 17: Showing effect of gender on CIMT in various studies

Study	Mohan et al.[13]	Sahoo et al.[4]	Present study
P	0.004	<0.001	<0.0001

CIMT: Carotid intima-media thickness

Table 18: Comparative P values of CIMT in diabetics and non-diabetics in different studies

Study	Sahoo et al.[4]	Mohan et al.[13]	Kawamori et al.[19]	Frauchiger B, Geroulakos et al.[15]	Pujia et al.[14]	Present study
P	0.0001	0.0001	0.001	0.004	0.001	<0.0001

CIMT: Carotid intima-media thickness

Effect of duration of DM on CIMT

In this study, there is positive correlation between duration of DM with CIMT value ($P = 0.001$). This study is correlating with the study by Mohan et al. ($P = 0.001$) [Table 20].

Effect of HbA1C on CIMT

In this study, there is positive correlation between HbA1C levels with CIMT ($P = 0.0004$) on comparing risk and non-risk group in DM subjects. This study is correlating with the study; Udaybaskaran et al. showed HbA1C had statistically significant positive correlation with CIMT [Table 21].

Effect of BMI on CIMT

In this study, there is positive correlation between BMI and CIMT ($P = 0.0006$). This study is correlating with study Sutton-Tyrrell et al. ($P = 0.001$) showed strong positive correlation of BMI with CIMT [Table 22].

CONCLUSION

- The present study showed increased values of CIMT in DM patients. Along with this risk factors such as age, HTN, BMI, and duration of DM, may actually have a correlation with CIMT either directly or indirectly influencing the disease process itself and contributing to atherosclerosis.
- USG-guided CIMT measurement is non-invasive, reproducible method for detecting of early arterial structural changes associated with various risk factors for atherosclerosis.
- The present study shows that CIMT increases with age, which is a non-modifiable risk factor for atherosclerosis and the correlation is statistically significant. Mean CIMT is significantly more in male cases (0.097 ± 0.04 cm) when compared to male controls (0.07 ± 0.02 cm) with $P < 0.0001$.
- The present study emphasized that as the duration of diabetes increases there is a progression of CIMT which is statistically significant.
- HTN an established risk factor for atherosclerosis is found to have a positive correlation with progression of CIMT which is statistically significant in the present study. BMI is shown to have statistical significance when compared between both study and control groups.
- The present study has demonstrated the role of traditional risk factors such as TC, HDL cholesterol, and TG in the progression of atherosclerosis but not found to have statistical significance with CIMT.

Table 19: Showing effect of HTN on CIMT in various studies

Study	Leary et al.[17]	Agarwal et al.[18]	Present study
P	0.01	0.05	0.04

CIMT: Carotid intima-media thickness, HTN: Hypertension

Table 20: Showing effect of duration of DM on CIMT in various studies

Study	Rathnakar shoo et al.[4]	Mohan et al.[13]	Pujia et al.[16]	Kawamori et al.[14]	Present study
P	0.04	0.001	0.05	0.03	0.001

CIMT: Carotid intima-media thickness, DM: Diabetes mellitus

Table 21: Showing effect of HbA1c on CIMT in various studies

Study	Udaybaskaran et al.	Yokoyama et al.[19]	Yamasaki et al.[20]	Present study
P	0.0004	0.01	0.03	0.0004

CIMT: Carotid intima-media thickness, HbA1C: Hemoglobin A1C

Table 22: Showing effect of BMI on CIMT in various studies

Study	Sutton-Tyrrell K et al.[21]	Stevens et al.[22]	Stevens et al.[23]	Present study
P	0.001	0.04	0.03	0.0006

CIMT: Carotid intima-media thickness, BMI: Body mass index

- The role of FBS and PPBS on CIMT is doubtful. This could be explained by due to the selection of the random values.
- There was a positive correlation of HbA1C with CIMT value among risk and non-risk group.
- Hence, measurement of CIMT by USG Doppler is reliable and helps in early medical intervention to take care of risk factors and lifestyle modification.

REFERENCES

1. Jadhav UM, Kadam NN. Carotid intima-media thickness as an independent predictor of coronary artery disease. Indian Heart J 2001;53:458-62.
2. O'Leary DH, Polak JF, Kronmal RA, Savage PJ, Borhani NO, Kittner SJ, et al. Thickening of the carotid wall. A marker for atherosclerosis in the elderly? Cardiovascular health study collaborative research group. Stroke 1996;27:224-31.
3. Baldassarre D, Amato M, Bondioli A, Sirtori CR, Tremoli E. Carotid artery intima-media thickness measured by ultrasonography in normal clinical practice correlates well with atherosclerosis risk factors. Stroke 2000;31:2426.
4. Sahoo R, Krishna MV, Subrahmaniyan DK, Dutta TK, Elangovan S. Common carotid intima-media thickness in acute ischemic stroke: A case control study. Neurol India 2009;57:627-30.
5. Park K. Parks Textbook of Preventive and Social Medicine. 19th ed. Jabalpur India: Banarsidas Bhanot Publishers; 2010. p. 280.
6. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the framingham population. Sixteen year follow-up study. Diabetes 1974;23:105-11.
7. Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW. Risk factors for stroke in middle aged british men. BMJ 1991;302:1111-5.
8. Touboul PJ, Elbaz A, Koller C, Lucas C, Adraï V, Chédru F, et al. Common carotid artery intima-media thickness and brain infarction: The etude du profil génétique de l'infarctus cérébral (GENIC) case-control study. The GENIC investigators. Circulation 2000;102:313-8.
9. Hatano S. Experience from a multicentre stroke register: A preliminary report. Bull World Health Organ 1976;54:541-53.
10. Chobanian AV. Vascular effects of systemic hypertension. Am J Cardiol 1992;69:3E-7E.
11. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC investigators. Stroke 1993;24:1297-304.
12. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: A population-based ultrasonography study in eastern Finnish men. J Intern Med 1991;229:225-31.
13. Mohan V, Ravikumar R, Shanthi Rani S, Deepa R. Intimal medial thickness of the carotid artery in south indian diabetic and non-diabetic subjects: The chennai urban population study (CUPS). Diabetologia 2000;43:494-9.
14. Pujia A, Gnasso A, Irace C, Colonna A, Mattioli PL. Common carotid arterial wall thickness in NIDDM subjects. Diabetes Care 1994;17:1330-6.
15. Frauchiger B, Schmid HP, Roedel C, Moosmann P, Staub D. Comparison of carotid arterial resistive indices with intima-media thickness as sonographic markers of atherosclerosis. Stroke 2001;32:836-41.
16. Allan PL, Mowbray PI, Lee AJ, Fowkes FG. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh artery study. Stroke 1997;28:348-53.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
18. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. N Engl J Med 1999;340:14-22.
19. Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. Diabetes Care 1992;15:1290-4.
20. Yokoyama H, Katakami N, Yamasaki Y. Recent advances of intervention to inhibit progression of carotid intima-media

thickness in patients with Type 2 diabetes mellitus. Stroke 2006;37:2420-7.

21. Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, *et al.* Carotid intima-media thickness in Japanese Type 2 diabetic subjects: Predictors of progression and relationship with incident coronary heart disease. Diabetes Care 2000;23:1310-5.

22. Sutton-Tyrrell K, Lassila HC, Meilahn E, Bunker C, Matthews KA, Kuller LH, *et al.* Carotid atherosclerosis in premenopausal and postmenopausal women and its association with risk factors measured after menopause. Stroke 1998;29:1116-21.

23. Stevens J, Tyroler HA, Cai J, Paton CC, Folsom AR, Tell GS, *et al.* Body weight change and carotid artery wall thickness. The atherosclerosis risk in communities (ARIC) study. Am J Epidemiol 1998;147:563-73.