

A STUDY OF THE FACTORS RELATED TO INTIMA-MEDIA THICKNESS OF THE COMMON CAROTID ARTERY AMONGST RURAL MIDDLE AGE INDIVIDUALS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Abstract. There is very little data regarding the factors related to intima-media thickness (IMT) of the common carotid artery in normal individuals in those with non-insulin diabetes mellitus and perimenopausal women in Southeast Asian countries. Ultrasound imaging evaluating the carotid artery IMT in those with diabetes and those on hormone replacement therapy (HRT) was performed beginning in August 2000 for a period of nearly two years at the Department of Radiology, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia. A total of 153 participants were included. Significant differences between the women on HRT and not on HRT were IMT and systolic blood pressure. When comparing those with non-insulin dependent diabetes mellitus (NIDDM) and normal individuals, the significant differences were IMT, total cholesterol level, systolic blood pressure and diastolic blood pressure. IMT was high in those with NIDDM but not in those on HRT. Both those with NIDDM and those on HRT had associated dyslipidemia and systolic hypertension.

INTRODUCTION

In Southeast Asia where large artery disease causing strokes is not as common as in Western countries, studies concerning this pathology are scarce. Most studies are quoted from Western literature where common carotid disease is more common than small artery disease.

A recent study in Malaysia on IMT in familial and non-familial hypercholesterolemia and its correlation to obesity was significantly associated with patients with abnormal body mass indexes and waist-hip ratios (Nafikudin *et al*, 2003). No Southeast Asian study has

dealt with an association between patients with diabetes mellitus or on hormone replacement therapy and IMT. The current study compared patients with non-insulin dependent diabetes mellitus and perimenopausal women with or without hormone replacement therapy (HRT) to normal individuals with regard to carotid artery disease in a rural setting.

PATIENTS AND METHODS

A cross-sectional study was conducted between August 2000 and May 2002 at the Department of Radiology, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, which is the only university hospital located in a rural community based setting in Malaysia.

Normal individuals, patients with non-insulin diabetes mellitus, perimenopausal women with and without hormone replace-

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ment therapy were included in the study.

Normal individuals were randomly selected from those who went to the radiology department for any radiological examination. Patients from the NIDDM group were recruited from those who were referred for any ultrasound examination. Perimenopausal women were recruited from those treated at the Menopause Clinic, Department of Obstetrics and Gynecology, Hospital Universiti Sains Malaysia.

Inclusion criteria for the normal group were those who had no major risk factors for atherosclerosis, including hypertension, diabetes mellitus, obesity, smoking or abnormal lipid levels.

Inclusion criteria for the NIDDM group were those with NIDDM who consented for carotid ultrasound examination.

Inclusion criteria for perimenopausal women were those with a normal blood pressure, random blood sugar, plasma lipids, a non-smoker and a normal serum estradiol level. They also consented to a carotid ultrasound examination. The patients on hormonal replacement therapy had to comply with treatment.

Exclusion criteria for the normal and NIDDM groups were those with a history of hypertension or smoking, obese patients, an abnormal blood pressure or abnormal lipid levels (dyslipidemia), preexisting vascular disease (eg vasculitis, connective tissue disease or Takayasu's disease), those who had undergone neck surgery, had previous radiotherapy of the head and neck region, a carotid endarterectomy or those with a history of cardiovascular or cerebrovascular disease prior to the study.

Exclusion criteria for perimenopausal women were those who had neck surgery, radiotherapy of the head and neck or carotid endarterectomy and those who had cardiovascular or cerebrovascular disease prior to study. The Research and Ethics Committee of the School of Medical Sciences, Universiti Sains

Malaysia gave ethical approval for this study.

Validity of the measurement tool

A validation study was carried out before proceeding to the actual study to evaluate the intimal thickness by different radiologists. Inter and intraobserver variation was evaluated. The validation study was conducted by the Department of Radiology, Hospital Universiti Sains Malaysia, Kubang Kerian (HUSMCK). The study subjects were volunteers randomly selected from workers. Forty subjects were included in the study, and measurements of intimal thickness of the common carotid artery (right and left) were done. All the subjects were free of major risk factors for atherosclerosis, such as hypertension, dyslipidemia, diabetes mellitus, smoking and obesity. They were also free of complications of atherosclerosis. Informed consent was then obtained. Each subject was examined twice, with one week between each exam. Each observer examined twenty subjects consecutively while alone with the patient in the scanning room. The observers were blinded to the other measurements. The observers involved were two radiologists and two trainee masters candidates in radiology who underwent training to become familiar with the technique. This validation was done to ensure that the technique used was acceptable, consistent and reproducible.

Method of examination

The common carotid ultrasound was carried out using an ATL Philips 3500, with a high frequency 5-12 MHz linear array transducer. The power output, focus, depth of measurement and gain were standardized by employing the preset program incorporated in the software package of the ultrasound equipment. The subjects were examined in a supine position with the neck extended. The probe was in the anterolateral position to the subject whose neck was extended. Prior to examination, the patients were allowed to rest

for at least 10 minutes so as to give full cooperation and reduce anxiety.

All measurements of intima-media thickness were made in the longitudinal plane at the point of maximum thickness on the far wall of the common carotid artery. The measurement was taken at a point about 1 cm proximal to the carotid bulb. The position of the carotid bulb is where the far wall deviated away from the parallel plane of the distal common carotid artery (Pujia *et al*, 1994).

The IMT was defined as the distance between the inner echogenic line representing the intima-blood interface and the outer echogenic line representing the adventitia-media junction. After freezing the image, the measurement was made with electronic calipers. Magnification of the ultrasound image was used to improve accuracy of placement of the calipers. Measurements were repeated three times, unfreezing the image on each occasion and relocating the position of maximal intima-media thickness. The mean of the three measurements was used for the IMT. The right and left common carotid arteries of each subject were analyzed separately. The observer was blinded to the use of hormone replacement therapy by the subjects.

The image orientation was in keeping with universally accepted conventions, longitudinal images were oriented with the subject's head on the left. The transverse images were oriented as if viewed from the subject's feet, hence the subject's right appears on the left side of the image. The subjects had a fasting lipid profile and fasting blood glucose before measurement of common carotid IMT.

The definitions of body mass index (BMI), plaque, presence of wall thickness defined as a measurement of more than 2 mm, hypertension, dyslipidemia, diabetes mellitus, premenopausal, postmenopausal and HRT followed the standard definitions in the literature (Bush *et al*, 1987; Prati *et al*, 1992; Pujia *et al*, 1994; Nabulsi *et al*, 1996; Bonora *et al*,

1997; Stensland-Bugge *et al*, 1997; Baron *et al*, 1998; Mast *et al*, 1998; Westendorp *et al*, 1999; Deurenberg-Yap *et al*, 2000; Glinsberg and Tuck, 2001; Mihmanli *et al*, 2002; Takahashi *et al*, 2004). The duration of hormone replacement therapy was for at least one year prior to the study.

A total of 161 candidates were recruited for the study. Eight candidates were excluded from the study due to a history of cardiovascular disease 5 and 3 were excluded due to a prior cerebrovascular accident. The remaining candidates (153) were then divided into 4 groups. The first group consisted of perimenopausal women who were not on HRT (non-HRT group) (n=50). The second group consisted of perimenopausal women who were on HRT (HRT group) (n=50). The third group consisted of patients with NIDDM (n=27) and the last group consisted of normal individuals (n=26).

Blood pressure, body weight and height were recorded on the day of examination. Clinical data for each subject was reviewed from their record. They had to have a fasting lipid profile and blood glucose prior to measuring common carotid IMT.

Statistical analysis

Statistical analysis was carried out, using the Statistical Package for Social Science version 11.0.

The coefficient of variation was calculated according to the formula $CV\% = (e/x)100$, where e is the mean of the absolute value of the difference between the observations of the 2 groups and x is the pooled mean value. The CV represents the interobserver error. The CV was 6.19% for the radiologists and 6.53% for the trainees.

RESULTS

Age was significantly different between the HRT and non-HRT groups ($t=3.02$, $p=0.003$). IMT of the common carotid artery was significantly different between the patients with

NIDDM and normal individuals ($t=6.40$, $p<0.001$) and between the HRT and non-HRT groups ($t=29.27$, $p<0.001$). The total cholesterol levels were significantly different between those with NIDDM and normal individuals ($t=4.62$, $p<0.001$). The systolic blood pressure was significantly different between those with NIDDM and normal individuals ($t=3.91$, $p<0.001$) and between the HRT and non-HRT groups ($t=4.11$, $p<0.001$). The diastolic blood pressure was significantly different between those with NIDDM and normal individuals ($t=4.12$, $p<0.001$). There

were no other significantly different variables amongst the groups (Table 1).

DISCUSSION

The mean IMT value for the NIDDM group was 0.75 mm (0.45-0.9 mm). In the HRT group, the mean IMT values for the right and left carotid arteries were 0.69 mm and 0.69 mm, respectively. The non HRT group had mean values of 0.80 mm and 0.86 mm for the right and left common carotid arteries, respectively. The mean IMT value for the common

Table 1
Comparison of parameters in those with NIDDM, without NIDDM, those on HRT and not on HRT.

Parameters and groups	n	Mean (SD)	t Statistic	p-value
Age				
NIDDM	27	50.70	1.77	0.084
Non-diabetes	26	48.23		
HRT	50	53.53	3.02	0.003
Non- HRT	50	56.90		
BMI				
NIDDM	27	24.95	0.013	0.989
Non-diabetic	26	24.94		
HRT	50	22.17	0.50	0.620
Non-HRT	50	22.44		
IMT				
NIDDM	27	0.75	6.40	<0.001
Non-diabetic	26	0.61		
HRT	50	0.69	29.27	<0.001
Non-HRT	50	0.80		
Total cholesterol				
NIDDM	27	179.66	4.62	<0.001
Non-diabetic	26	166.92		
HRT	50	178.31	0.87	0.388
Non-HRT	50	179.59		
SBP				
NIDDM	27	123.96	3.91	<0.001
Non-diabetic	26	118.92		
HRT	50	101.18	4.11	<0.001
Non-HRT	50	110.08		
DBP				
NIDDM	27	82.33	4.12	<0.001
Non-diabetic	26	78.04		
HRT	50	69.98	-0.73	0.470
Non-HRT	50	69.56		

NIDDM – Non-insulin dependent diabetes mellitus; HRT- Hormone replacement therapy

carotid arteries was 0.69 mm in the HRT group and 0.80 mm in the non-HRT group.

Our study found that common carotid IMT was significantly greater in patients with NIDDM than in healthy subjects. This is in agreement with previous studies. Pujia *et al* (1994) reported IMT in the common carotid was thicker in patients with NIDDM than in controls. Studies by Niskanen *et al* (1996) and Bonora *et al* (1997) also reported similar findings. The difference between those studies and this study is patients in those studies had other associated risk factors, including hypertension, dyslipidemia, obesity and smoking, whereas our study excluded these factors. The reason for the high IMT in patients with NIDDM is probably related to high insulin levels (Niskanen *et al*, 1996). Our study showed that even without major risk factors, patients with NIDDM had high IMT levels which means they are at high risk for cerebrovascular complications.

The age range for patients with NIDDM in this study was 40-60 years old. This reflects the high prevalence of NIDDM in this age group. The BMI range for patients in this study was 21.67-29.17 kg/m². Fifty-one point eight percent of patients with NIDDM were overweight, none were obese. The mean BMI for patients with NIDDM was 24.95 (range 22.64-28.25). Being overweight is not unusual in patients with NIDDM. In the Second National Health and Morbidity Survey conducted by the Ministry of Health Malaysia (1997), 7.5% of diabetic patients were found to be overweight and 11.3% were obese.

In this study, blood pressure was higher in patients with NIDDM. This could again be explained by the fact that most patients were in an older age group, which is strongly associated with a higher blood pressure (Staessen *et al*, 2003). Subjects with NIDDM were found to have a higher mean systolic blood pressure (123.96 mmHg) and diastolic blood pressure (82.33 mmHg) than the non-diabetic

group (mean systolic blood pressure 118.92 mmHg and mean diastolic blood pressure 78.04 mmHg). The fasting cholesterol (mean 179.67 mg/dl) and triglyceride levels (mean 149.63 mg/dl) in the patients with NIDDM were significantly higher ($p < 0.001$) than those of the control group, although they were in the normal range.

The non-HRT group had a higher mean systolic blood pressure than the HRT group. This may be due to a lack of estrogen effect on the vessels, as these women were not on hormone replacement therapy.

This cross-sectional study showed that hormone replacement therapy use was associated with lower IMT in the common carotid artery. The results of this study support the results of a previous study showing that hormone replacement therapy led to a delay in thickening of the intima-media. Le Gal *et al* (2002) on their longitudinal study found that hormone replacement therapy was associated with a lower IMT in the common carotid arteries and a lower prevalence of carotid atherosclerotic plaques. Women who had surgical menopause had an increased IMT if they did not receive HRT (Mihmanli *et al*, 2002).

The association between HRT use and IMT was significant and independent of serum total cholesterol, BMI, smoking, hypertension and NIDDM. The numerous biological effects of estrogens are consistent with atheroprotection. Estrogens decrease total and LDL cholesterol, lipoprotein and increase HDL cholesterol. They inhibit lipoprotein oxidation and arterial smooth muscle cell proliferation and have favorable effects on soluble markers of vascular inflammation, vascular stiffness and endothelium-dependent vasodilatation.

In conclusion, this study in rural Malaysians supports the findings in the West that high cholesterol levels and systolic hypertension are associated with carotid artery disease. No long-term follow-up was performed on these patients to evaluate disease progression

to stroke. A long-term prospective study with a larger group of patients is needed before significant conclusions can be drawn.

REFERENCES

- Baron YM, Galea R, Brincat M. Carotid artery wall changes in estrogen treated and untreated post-menopausal women. *Obstet Gynecol* 1998; 91: 982-6.
- Bonora E, Tessari R, Micciolo R, *et al.* Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients. Relationship with insulin resistance. *Diabetes Care* 1997; 20: 627-31.
- Bush TL, Barret-Connor E, Cowaq LD, *et al.* Cardiovascular motility and noncontraceptive use estrogen in women: results from the lipid research clinics program follow up study. *Circulation* 1987; 75: 1102-9.
- Deurenberg-Yap M, Schmidt G, Van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. *Int J Obes Relat Metab Disord* 2000; 24: 1011-7.
- Glinsberg HN, Tuck C. Diabetes and dyslipidemia. *Heart Fail Monit* 2001; 2: 14-20.
- Lu M, Shi LJ, Shi P, Kang S, Wu LX, Wu YF. Hypertension and subclinical carotid atherosclerosis in a general population of a rural areas in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; 25: 841-4.
- Le Gal G, Gourlet V, Hogrel P, plu-Bureau G, Pierre-Jean T, Pierre-yves S. Hormone replacement therapy use is associated with a lower occurrence of carotid arteriosclerotic plaque but not with media thickness progression among postmenopausal women. The vascular aging (EVA) study. *Atherosclerosis* 2002; 166: 163-70.
- Mast H, Thompson JLP, Lin IF, *et al.* Cigarette smoking as a determinant of high-grade carotid artery stenosis in hispanics, black, and white patients with stroke or transient ischaemic attack. *Stroke* 1998; 29: 908-12.
- Mihmanli V, Mihmanli I, Atakir, *et al.* Carotid intima-media thickness in surgical menopause: women who received HRT versus who did not. *Maturitas Eur Menopause* 2002; 42: 37-43.
- Ministry of Health, Malaysia. Report presented at the National Health Morbidity Survey II Conference, 20-22 November 1997, Kuala Lumpur: Ministry of Health, 1997.
- Nabulsi AA, Folsom AR, Szklo M, White A, Higgins M, Heiss G. No association of menopause and hormone replacement therapy with carotid artery intima-media thickness. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation* 1996; 94: 1857-63.
- Nafikudin M, Nawawi H, Muid S, Annuar R, Yusoff K, Khalid BA. Measurement of intima-media thickness of common carotid arteries using ultrasound in patients with familial and non-familial hypercholesterolaemia and correlation of intima-media thickness to obesity. *Med J Malaysia* 2003; 58: 647-52.
- Niskanen L, Rauramaa R, Miettinen H, Haffner SM, Mercuri M, Uusitupa M. Carotid artery intima-media thickness in elderly patients with NIDDM and in nondiabetic subjects. *Stroke* 1996; 27: 1986-92.
- Prati P, Vanuzzo D, Cassaroli M, *et al.* Prevalence and determinants of carotid atherosclerosis in a general population. *Stroke* 1992; 23: 1705-11.
- Pujia A, Gnasso A, Irace C, Colonna A, Mattioli PL. Common carotid arterial wall thickness in NIDDM subjects. *Diabetes Care* 1994; 17: 1330-6.
- Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. *Lancet* 2003; 361: 1629-41.
- Stensland-Bugge E, Bonna KH, Joakimsen O. Reproducibility of ultrasonographically determined intima-media thickness is dependant on arterial wall thickness. The Tromso Study. *Stroke* 1997; 28: 1972-80.
- Takahashi K, Tanaka E, Murakami M, *et al.* Long-term hormone replacement therapy delays the age related progression of carotid intima-media thickness in healthy postmenopausal women. *Maritutas*. 2004; 49: 170-7.
- Westerdorp IC, Veld BA, Bots ML, Akkerhuis JM, Hofman A, Grobbee DE. Hormone replacement therapy and intima-media thickness of the common carotid artery: the Rotterdam study. *Stroke* 1999; 30: 2562-7.