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

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Summary

Ultrasonographic measurements of the intima-media thickness (IMT) of common carotid arteries (CCA) were taken in 50 patients with familial hypercholesterolaemia (FH) and 57 patients with non-familial hypercholesterolemia (NFH). The lipid profile, body mass index (BMI) and waist-hip ratio (WHR) of each patient were recorded. In FH patients, the IMT was significantly higher in overweight and elevated WHR subgroups compared to the normal with significant correlations between BMI and WHR to the IMT. In NFH patients, the IMT was significantly higher in the elevated WHR compared to the normal subgroup but the correlations between either BMI or WHR to IMT were insignificant. These suggest that the environmentally modified anthropometric indices may have an effect on atherosclerosis in genetically determined hypercholesterolaemia in FH patients.

Key Words: Ultrasound, Intima-media thickness, Atherosclerosis, Hypercholesterolaemia, Body mass index, Waist-hip ratio

Introduction

The purpose of this paper is to highlight our local study in using B-mode ultrasound to measure the intima-media thickness (IMT) of the common carotid arteries (CCA) in patients with familial hypercholesterolaemia (FH) and non-familial hypercholesterolaemia (NFH) and to correlate the IMT to obesity.

The invention of ultrasound gray-scale imaging has allowed the radiologists to image the blood vessels almost from the start because the fibrous vessel walls are excellent reflectors and are readily visible on ultrasound. With the advent of new computer technology and improvement of the image quality, one can also visualise the structures in the vessel walls such as the tunica intima and tunica media in better detail using ultrasound.

Over the past decade, measurement of IMT using high-resolution ultrasonography has emerged as one of the methods of choice for determining the anatomic extent

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of atherosclerosis and its progression in the vessels[1]. *In vitro and in vivo* studies showed that carotid artery IMT measurements obtained by ultrasound correlated very well with pathologic measurements[2]. Numerous investigators have demonstrated the reproducibility of this technique [3].

Atherosclerosis is a common arterial disorder in hypercholesterolaemia, which has a known association with obesity. Obesity can be determined by measuring body mass index (BMI) and waist-hip ratio (WHR)[4]. Elevated WHR indicates central obesity. The correlation of IMT to obesity is determined using these data.

Materials and Methods

This study was conducted in Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, from January 2000 to December 2001. The study subjects were recruited among the patients who attended the Specialist Clinics at Hospital UKM and the staff of the university who volunteered for the study. All these patients were known to have hypercholesterolemia either from their previous blood tests or from the family history of hypercholesterolaemia. Informed consent was obtained from every patient and approval by the institutional Ethical Committee was also obtained before starting the study.

All patients undertook a screening protocol consisting of clinical history, physical examination and laboratory tests including fasting lipid profiles, glucose, renal profile, liver function tests, and thyroid function tests. The patients were excluded from the study if they had diabetes mellitus, renal, liver, or endocrine diseases and also those with known secondary causes of hypercholesterolaemia. The inclusion criteria for definite and possible FH were based on the Simon Broome's register for FH (Table I). NFH was defined as those with total cholesterol (TC) more than 6.5 mmol/l and/or low density lipoprotein-cholesterol (LDL-C) more than 3.8 mmol/l but did not fulfil Simon Broome's criteria for definite or possible FH [5].

BMI was calculated using the formula, BMI = Weight (Kg)/ Height ^{2} (m^2). WHR was determined by taking the ratio of the circumference at midway between the inferior margin of the last rib and the iliac crest in horizontal plane to the hip circumference around the pelvis at the point of maximal protrusion of the buttock. Based on the BMI, the patients were divided into overweight/obesity (BMI $\geq$ 25) and normal subgroup (BMI < 25). Based on the WHR, they were divided into the elevated WHR subgroup (WHR > 0.9 in males and WHR > 0.8 in females), and normal WHR subgroup (WHR $\leq$ 0.9 in males, WHR $\leq$ 0.8 in females).

The ultrasound machine, Aloka SSD-2000 (Aloka Co., Ltd, Japan) equipped with 7.5MHz linear transducer was used to measure the IMT. The patients were asked to lie down in supine position with a pillow under the lower neck and shoulders. In this position, the neck would be slightly extended so that the common carotid arteries would be easily accessible.

The IMT was identified on ultrasound by the presence of the double lines pattern consisting of two parallel echogenic interfaces in the far wall of the common carotid arteries with the first one between the blood and the tunica intima and the other between the tunica media and the tunica adventitia (Figure 1 & 2). The IMT of the far wall of both the right and left common carotid arteries were measured at the point 1.0cm, 2.0cm, and 3.0cm proximal to the carotid bifurcation. The average measurement of the IMT was then calculated in each patient. The data statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 10 software on an IBM compatible computer..

Results

There were 107 patients included in the study. They consisted of 50 FH patients (19 males and 31 females; 38 Malays, 11 Chinese and 1 Indian; mean age ± SD: 42.8 ± 12.1 years), and 57 NFH patients (28 males, 29 females; 44 Malays, 12 Chinese and 1 Indian; mean age ± SD: 49.0 ± 8.1 years). Among the 50 FH patients, 43 were categorised as definite FH while the remaining 7 were possible FH patients.

The serum total cholesterol and LDL-C levels were significantly higher in FH compared to NFH (Table II). Among the FH patients, the IMT of the overweight subgroup was 0.74 ± 0.21mm compared to the non-overweight subgroup, which was 0.67 ± 0.17mm ($p<0.05$). Similarly, the FH patients with elevated WHR subgroup had significantly higher IMT compared to the normal WHR subgroups (Table III).

Among the NFH patients, the IMT of the elevated WHR subgroup was 0.72 ± 0.14mm compared to the subgroup with normal WHR, which was 0.66 ± 0.10mm ($p<0.05$). There was no significant difference in the IMT between the overweight and non-overweight subgroups in NFH patients. In the FH patients, the correlations between IMT and BMI was, r = 0.188 ($p<0.005$) and between IMT and WHR was, r = 0.189 ($p<0.005$). In the NFH patients there were no significant correlations noted between either BMI or WHR and the IMT.

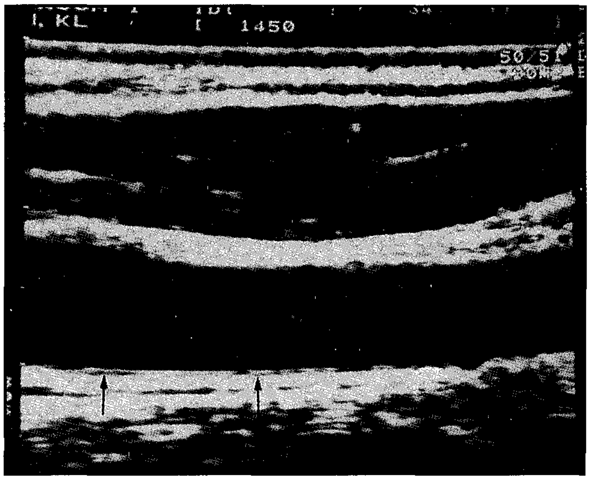

Fig. 1: Normal thickness and appearance of the combined tunica intima and media of the common carotid artery. The hypoechoic line separates the tunica media from tunica adventitia (arrows)

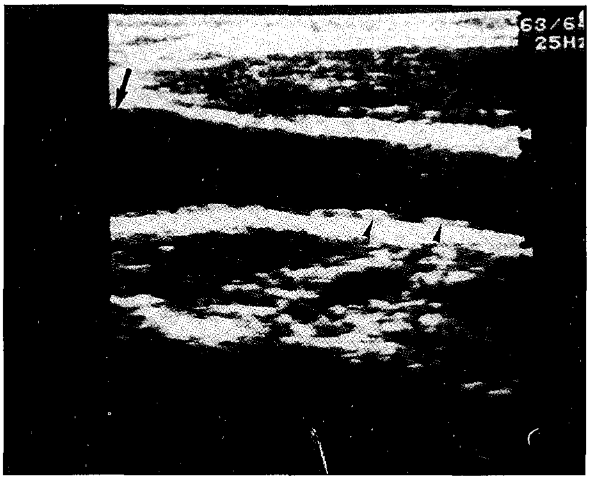

Fig. 2: Slightly thickened tunica intima and media of the common carotid artery measuring 0.8 - 1.0 mm (arrowheads). The carotid bulb is seen distal to this level (arrow).

Table I: The criteria for classification of hypercholesterolaemia based on Simon Broome's criteria for familial hypercholesterolaemia

Definite Familial Hypercholestrolaemia	Possible Familial Hypercholestrolemia
TC > 7.5 mmol/l and/or	TC > 7.5 mmol/l and/or
LDL-C > 4.9 mmol/l if age > 16 years.	LDL-C > 4.9 mmol/l if age > 16 years.
(TC > 6.5 mmol/l if age < 16 years).	(TC > 6.5 mmol/l if age < 16 years).
Tendon xanthoma(ta) in 1 or more of	**Plus**
family members i.e. either in the patient or	Family history of premature coronary artery disease in
parents, children, siblings, uncles, aunts or	first-degree relative (< 60years) or
grandparents	second-degree relative (< 50years) or
	TC > 7.5 mmol/l and/or
	LDL-C > 4.9 mmol/l if age > 16 years.
	(TC > 6.5 mmol/l if age < 16 years)
	Plus
	Family history of severe
	hypercholesterolaemia (TC >7.5mmol/l in
	first or second-degree relatives)

Non-Familial Hypercholestrolaemia
TC > 6.5 mmol/l and/or LDL-C > 3.8 mmol/l with no other criteria of definite or possible FH

Table II: Serum lipid profiles of patients with familial and non-familial hypercholesterolaemia

Parameters	Familial Hypercholesterolaemia (n = 50)	Non-familial hyppercholestrolaemia (n = 57)	p
Age (years)	42.8 ± 12.1	48.0 ± 8.1	(NS)
Males : Females	19 : 31	28 : 29	(NS)
Total Cholesterol (mmol/l)	9.1 ± 2.0	7.1 ± 0.8	< 0.0001
Low-density lipoprotein (mmol/l)	6.8 ± 1.9	4.8 ± 0.9	< 0.0001

NS = Not significant

Table III: The intima-media thickness of patients with normal and elevated WHR and with normal BMI and overweight

	Measurements of IMT (mm)		p
	Normal WHR	Elevated WHR	
FH Patients (n = 50)	0.66 ± 0.12	0.74 ± 0.22	<0.05
NFH Patients (n = 57)	0.66 ± 0.10	0.72 ± 0.14	<0.05
	Normal BMI	Overweight	
FH Patients (n = 50)	0.67 ± 0.17	0.74 ± 0.21	<0.05
NFH Patients (n = 57)	0.68 ± 0.13	0.70 ± 0.13	0.67

Discussion

Ultrasound measurement of the IMT of the CCA is very important from a practical point of view. It is a non-invasive technique capable of visualising the structures within the vessel lumen, or in the wall where the formation of atherosclerotic plaques takes place, and also outside the wall. It was proven to be extremely safe, usually well accepted by the patients and inexpensive.

Although many studies on IMT of the carotid arteries had been reported in the literature, data on our population is limited. It was noted that, there were important differences in the techniques of measurement of the carotid IMT between experts in the field. The lack of standardisation of this technique has been a major barrier to a more extensive use in research or clinical practice. Recently, workers in this field were reported to be trying to come up with the agreement on the details pertaining to the ultrasound techniques. A review on the information of the IMT measurements in normal subjects was done to create a framework that can be used to define an abnormal result[6]. The availability of the normal reference values would become the important step toward increased use of the ultrasound technique. Currently, computer software or PC-base softwares are being developed in several laboratories to measure the IMT automatically with more accurate reading than the manual techniques, so that the inter- and intra-observer variability can be minimised.

The ultrasound technique employed by us restricted the measurement of the IMT to the far wall of the distal 3.0cm segments of the common carotid arteries, proximal to the bifurcations. Taking the measurement at the point of the bifurcation of the carotid arteries will give inaccurate result due to presence of physiological thickening at this point. Previous researchers had measured the IMT at several other sites along the carotid vessels, such as at the carotid bulb, and at the proximal internal carotid arteries. The far wall offers the optimal geometric conditions for obtaining a high precision and reproducibility rate of ultrasound measurement. Wong and co-workers had shown that the ultrasound measurement of the IMT of the far walls did not provide significant different results from that obtained from histology[7].

The ultrasound machines with Doppler facilities and electrocardiographic tracing are also capable of measuring luminal diameter of the vessels in relation to the cardiac cycle and the flow velocity of the blood. This technique had been used to estimate endothelial function by measuring vascular relaxation in response to shear stress [8].

The data on the carotid artery IMT is very useful in assessing the vascular wall changes in response to treatment for hypercholesterolaemia. It was reported that lipid-lowering therapy had successfully reduced the thickness of the IMT [9]. Similarly, the increase in IMT of the carotid arteries was considered to reflect early atherosclerosis, although it might also reflect adaptation to the other factors, such as hypertension. Several authors had shown a true correlation between an increase in IMT and atherosclerosis and also a strong correlation between an increase in IMT and coronary heart disease[10,11]. Recent prospective studies have clearly demonstrated that the ultrasound measurements of the carotid artery IMT could also be used as potent predictors of myocardial infarction and stroke, even after adjustment for other risk factors[12,13].

Hypercholesterolaemia is common in obese individuals. Majority of the obese individuals were found to have elevated levels of serum triglyceride and depressed levels of high-density lipoprotein cholesterol (HDL-C)[14]. This finding has became the basis of our study for the correlation of the BMI and WHR to the IMT in our local population with hypercholesterolaemia.

The results of serum lipid tests were comparable to the previous study, which indicated that the FH patients had significantly higher level of serum TC and serum LDL-C compared to NFH patients [15,16]. Similarly, the IMT of FH patients who were overweight and having elevated WHR was found to be significantly higher than the NFH patients. Regarding correlations between IMT and BMI and between IMT and WHR, the value of r indicated significant correlation in FH patients. Interestingly, the correlation between either BMI or WHR to the IMT in the NFH patients was found to be insignificant.

In conclusion, the data on IMT from ultrasound imaging of the carotid arteries would provide useful and reliable information regarding the presence and extent of atherosclerosis in patients with hypercholestrolemia. Elevated BMI and central obesity were associated with increased IMT in FH patients but this association was less clear in NFH patients. These suggest that the environmentally modifiable anthropometrics indices may have an effect on the progression of atherosclerosis in genetically determined hypercholesterolaemia in FH patients.

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