ORIGINAL ARTICLE

Carotid Intima Media Thickness and High Sensitivity C-Reactive Protein as Markers of Cardiovascular Risk in a Malaysian Population

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SUMMARY

Introduction: Carotid intima media thickness (CIMT) being a cost effective and easily performed technique is useful in the detection of subclinical atherosclerosis and has been shown to be a prognosticator of cardiovascular events. The primary objective of this study was to obtain the distribution of CIMT measurements, highly sensitive C reactive protein (hs-CRP) and assessing health awareness and attitudes of the Malaysian population at cardiovascular disease (CVD) risk and not receiving lipid lowering agents. Secondarily the study sought to assess the significance of the relationship between these measurements against various patient characteristics.

Methods: Measurements of CIMT are obtained by ultrasonography of 12 sites within the common carotid artery was recorded for 123 subjects from a single centre tertiary hospital of Malaysia who had two or more CVD risk factors but were not receiving lipid lowering therapy. CVD risk factors and lipid and glucose profiles were analyzed with respect to distribution of CIMT and high-sensitivity C-reactive protein (hs-CRP) values.

Results: The mean-max CIMT was 0.916±0.129mm (minimum 0.630mm, maximum 1.28mm) and the mean-mean CIMT was 0.743±0.110mm (minimum 0.482mm, maximum 1.050mm) and mean hs-CRP was 0.191mg/dL (minimum 0.030mg/dL, maximum 5.440mg/dL). Multivariate analyses confirmed a significant association between increasing CIMT and increasing age, total and low density lipoprotein cholesterol while log-transformed hs-CRP levels showed significant association with increasing body mass index, waist circumference, high blood glucose and triglyceride levels. Our patients had good health awareness on CVD.

Conclusion: Newly defined CIMT measurements and hs-CRP levels may be useful adjunctive tools to screen for atherosclerosis in the Malaysian population. It may help in refining risk stratification on top of traditional clinical assessment.

KEY WORDS:
Atherosclerosis, Carotid Intima-Media Thickness, C-Reactive Protein, Risk Factors, Malaysia,

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity in Malaysia accounting for about 35000 admissions in 2001 and responsible for 25% of all hospital mortality in Ministry of Health (MOH) hospitals [1]. The Fourth National Health and Morbidity Survey[2] (NHMS) reported an astounding prevalence rate of overweight and obese adults at 44.5%, diabetes mellitus at 20.8%, hypercholesterolaemia at 35.1% and hypertension at 32.7%. A significant proportion of these risk factors were subclinical. Due to the insidious onset of atherosclerosis and consequent CVD the first presentation of which is fatal in 30-50% of the time[3-5] correctly identifying at risk patients is paramount to instituting preventive measures and reducing healthcare costs.

Carotid artery intima media thickness (CIMT) evaluation by ultrasound allows an easy, safe, non-invasive and cost effective method to detect subclinical atherosclerosis and has been shown to be a prognosticator of cardiovascular events [6-8]. Its use has progressed from being a mere research tool to becoming an accepted clinical modality for assessing moderate risk subjects and refining risk stratification. The utility of CIMT as a screening tool has found its way into various guidelines such as the SHAPE I, American Society of Echocardiography 2006 and more recently the AHA/ACCF 2010 guidelines on the assessment and prevention of cardiovascular disease[9-11]. According to a recently published study of more than 10000 patients with a mean follow up of 15.2 years, a simple common carotid artery (CCA) CIMT measurement was as good as a more comprehensive measurement of CIMT in all carotid segments and plaques. In addition, both methods were superior as a 10 year CVD risk prediction model compared to traditional risk factors alone [12].

Although there is an abundance of CIMT research data for the Caucasian population, insights into at risk Asian populations and more pertinently the Malaysian population with subclinical CVD are still lacking. To date, the only published normal CIMT values in Asians are those of the rural Korean population aged 40-70 years [13]. Small studies have shown that normal CIMT measurements differ across Caucasian, Caribbean, African and South Asian ethnicities independent of age or cardiovascular risk factors[14,15]. There is still a significant lack of information about at risk

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populations and whether differences exist across regions and countries in Asia.

Metabolic syndrome is considered to be a pro inflammatory state predisposing an individual to higher CVD risk [16]. High sensitivity C-reactive protein (hs-CRP) is an inflammatory marker and its production thought to be mediated via interleukin 6 (IL-6) produced by visceral adipocytes[17]. Past studies have shown that higher levels of hs-CRP were associated with various components of the metabolic syndrome[18,19]. The JUPITER study published in 2006 showed mortality and morbidity benefits in treating patients at moderate risk with high hs-CRP levels >0.2mg/dL independent of LDL levels [20].

This paper presents data for the Malaysian cohort of patients included in a large pan-Asian cross-sectional observational study, which strived to bridge the clinical data gap by primarily defining the CCA CIMT for a Malaysian population with 2 or more cardiovascular risk factors not on any lipid lowering therapy. Secondarily, the study examined the associations of various demographic characteristics, CVD risk factors and hs-CRP with CIMT values. Lastly the subjects' prevailing health awareness and attitudes were assessed via a questionnaire. The findings of the complete study (Reference number D3560L00092) have been published in the International Journal of Cardiology [21].

MATERIALS AND METHODS

This study is conducted in accordance to principles of International Conference on Harmonization/Good Clinical Practice (ICH/GCP) and approved by Medical Research Ethics Committee. This cross sectional observational sub-study was part of a larger regional Asia wide study involving 7 other countries namely China, Indonesia, Korea, Philippines, Taiwan, Thailand and Vietnam involving >2500 patients, the results for which have been published as mentioned above. In total, 123 consecutive adult subjects aged 18-69 years were enrolled after provision of informed consent from a single centre at Sarawak General Hospital, Malaysia. Patients were to have at least 2 or more traditional CVD risk factors namely age ≥45 years for males and ≥55 years for females, history of premature CVD or sudden deaths in first degree male relative of ≤55 years and female relative of ≤65 years, any cigarette smoking in the past month, hypertension and low high density lipoprotein (HDL-C) <1mmol/L and not on any lipid lowering drug for the last 3 months. The exclusion criteria were subjects with established coronary artery disease (CAD) defined as presence of any history of myocardial infarction, myocardial ischaemia, angina whether stable or unstable and history of coronary revascularisation procedures done. CAD equivalent states such as diabetes mellitus were deemed to be a risk factor and not specifically excluded in this study.

Any conditions that may possibly affect hs-CRP levels were excluded such as arthritis, infection, renal and liver function impairment, recent tissue injury, recent major surgery, women on hormonal replacement therapy and use oral non steroidal anti-inflammatory drugs in the preceding 3 months. Other non clinical exclusion criteria include personnel and staff involved in the trial and subject participation in any trial in the preceding 3 months.

Study Design

The pre-specified primary objectives of this study was firstly to define the CCA CIMT and hs-CRP values for a Malaysian population with 2 or more cardiovascular risk factors not on any lipid lowering therapy and secondly to determine the subjects' prevailing awareness and attitudes towards CVD risks and treatment. The post hoc secondary objective of the study was to determine the associations of various demographic characteristics, CVD risk factors and hs-CRP with CIMT values. Upon obtaining informed consent a physical examination was performed followed by collection of demographic data and fasting blood samples for total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), glucose and hs-CRP. A questionnaire assessing subjects' health awareness, prevailing attitudes and behaviour on cardiovascular health matters is then completed by the subjects. Depending upon the availability of our sonographer, previously trained and certified in CIMT measurement, subjects will either have their CIMT measured in this one and only visit or at a second final visit (Figure 1).

Questionnaire

A questionnaire (as seen in Table V with results) is completed by the subjects after completion of physical examination, demographic data collection and blood sampling. The questionnaire had a total of 18 questions addressing awareness of modifiable and non modifiable cardiovascular risk factors, cardiovascular disease, the information sources by which subjects most often obtained them and subjects' attitudes towards preventive measures to address these risk factors.

CIMT measurement method

CIMT measurement was performed using a high resolution B-mode ultrasonography system (M-Turbo; SonoSite Inc, Bothell, WA, USA), a dedicated HFL38x phased array 13MHz transducer and has a customised SonoCalc Embedded IMT software. Each of the left and right CCA was scanned separately from 3 positions namely anterior, lateral and posterior to get an accurate representation of the burden of atherosclerosis in the carotid arteries. CIMT measurements were done in the distal CCA avoiding the distal most portion where it begins to dilate into the bulbous area prior to the bifurcation into external and internal carotid arteries. Measurements of CIMT were acquired across a 10mm length from the near as well as far carotid wall hence giving 6 measurements per side and a total of 12 per subject (Figure 2). The software has automated CIMT measurement and calculation capabilities (taking into account all 12 measurements) the average, max and min for the mean values, and average, max and min for max region values.

Statistical analysis

The Mean-Mean and Mean-Max CIMT measurements obtained and the hs-CRP levels were subjected to descriptive statistical analysis. The association between CIMT values with demographic characteristics, CVD factors, lipid values and hs-CRP were examined by one-way analysis of variance (ANOVA) models, simple regression models in a univariate approach and by general linear models in a multivariate approach. The per protocol analysis set (PPS) from available data was used for analysis. It included subjects who did not

violate inclusion and exclusion criteria and whose CIMT values were available.

The association of the Mean-Max and the Mean-Mean CIMT measurements using ANOVA against various age groups was firstly looked at. This was followed by analysis of association of gender and the various other traditional risk factors such as body mass index (BMI), history of cigarette smoking, hypertension, diabetes mellitus and family history. Subjects were divided into 3 groups according to their BMI, less than 25 being normal, 25-29.9 being overweight and 30 or more being obese. Current cigarette smoking status was defined as any consumption in the last one month. A subject was deemed to be a hypertensive or a diabetic if he or she was on pharmacotherapy or blood pressure of 140/90mm Hg and fasting glucose of 7.0mmol/L or more in treatment naïve patients. The available data from the study subjects were all of normal or low HDL-C hence high HDL-C, a negative CVD risk predictor was not analysed.

Secondly a similar association was looked for with the various metabolic syndrome features, such as abdominal obesity defined by waist circumference of more than 90cm for male subjects and more than 80cm for female subjects, elevated triglycerides of more than 1.7mmol/L, low HDL-C defined as less than 1.0mmol/L for men and 1.3mmol/L for women and lastly impaired fasting glucose defined as being in the range of 5.6-6.9mmol/L. Lastly the hs-CRP was similarly analysed employing the log value of the obtained results. In the final part of the analysis we subjected the Mean-Max and the Mean-Mean CIMT and the log hs-CRP values to a simple linear regression analysis, determined the Pearson's correlation coefficient and lastly performed a multivariate analysis using a general linear model.

RESULTS

Demographic data

The study successfully enrolled 123 eligible subjects of multiethnic origin reflecting the urban population of Kuching, Sarawak, Malaysia from 2009 to 2010. The mean age was 55±7.8 years being made up of mostly males and those in between 50-69 years old. The most common cardiovascular risk factor in our population was age with a prevalence of nearly 90% and more than two thirds had hypertension. Hence it was not surprising that our population cohort being middle aged urban dwellers, more than half of them had abdominal obesity and nearly two thirds were obese or overweight being significantly higher than the national prevalence rate of 44.5% as was reported in the 4th NHMS. Smoking prevalence comprised more than a third of the study population and the rest of the patient characteristics are shown in Table I. However there exists an element of selection bias being predominantly conducted from a tertiary hospital located in an urban area.

Mean-Max and Mean-Mean CIMT results

For each individual subject, the mean of 12 CIMT measurements were calculated. The overall mean of this mean CIMT (mean-mean CIMT) is obtained for each subject and its frequency in each category of 0.01mm increments is plotted on a histogram (Figure 3). The mean of the maximum value of CIMT measured is then similarly calculated (mean-max CIMT) and values plotted onto a second histogram (Figure 4).

The mean of the Mean-Max CIMT measurement was 0.916±0.129mm (minimum 0.630mm, maximum 1.28mm). There is a Gaussian distribution of the CIMT values and most of the study subjects with 2 or more risk factors had Mean-Max CIMT values between 0.7 to 1.1mm. The mean of the Mean-Mean CIMT measurement was nearly 0.2mm less than the Mean-Max CIMT value at 0.743±0.110mm (minimum 0.482mm, maximum 1.050mm) and most were in the range of 0.6 to 0.9mm. The mean hs-CRP level was 0.191mg/dL (minimum 0.030mg/dL, maximum 5.440mg/dL).

Table I: Baseline characteristics of study population (based on per protocol analysis set)

Characteristics	Mean (SD)	Range
Age, years	55.6 (7.8)	22 - 68
Waist circumference, cm	88.9 (10.1)	66 -126
Sitting SBP, mmHg	140.8 (19.7)	99 -187
Sitting DBP, mm Hg	85.6 (12.4)	56 -118
Body weight, kg	69.1 (13.6)	43.7 -129
Height, cm	161.3 (9.2)	140 -180
Body mass index, kg/m^2	26.5 (4.2)	17.9-43.3
Total cholesterol	5.66 (2.0)	2.95-8.64
LDL-cholesterol	3.57 (1.67)	0.91-5.33
HDL-cholesterol	1.32 (0.63)	0.75-2.40
Triglycerides	4.25 (5.0)	1.45-20.2
Glucose	5.43 (1.0)	4.01-11.44
	Number	**Percentage**
Age (men >= 45 years, women >= 55 years)	108	87.8
Hypertension	90	73.2
Abdominal obesity (men ≥90cm, women ≥80cm)	72	58.5
BMI categories		
Normal (<25)	44	35.8
Overweight (25-<30)	58	47.1
Obese (≥30)	21	17.1
Cigarette smoking (any in the last 1 month)	47	38.2
Family history of premature CVD	18	14.6
Low HDL-C	8	6.7
Diabetes mellitus	5	4.1

Table II: Descriptive statistics of mean-max and mean-mean CIMT value (mm) and hs-CRP by subject characteristics

	n	Mean-Max CIMT (mm)		Mean-Mean CIMT (mm)		log hs-CRP	
		Mean	p value	Mean	p value	Mean	p value
Age			<0.0001		<0.0001		0.58
<29	2	0.631		0.501		0.251	
30-39	4	0.759		0.595		0.160	
40-49	16	0.868		0.703		0.140	
50-59	60	0.920		0.745		0.217	
60-69	41	0.958		0.780		0.178	
Gender			0.23		0.30		0.42
Male	74	0.927		0.751		0.179	
Female	49	0.899		0.730		0.209	
BMI (kg/m^2)			0.43		0.58		0.01
Normal weight (<25)	44	0.896		0.729		0.165	
Overweight (25-<30)	58	0.929		0.752		0.173	
Obese (>=30)	21	0.921		0.745		0.340	
Cigarette Smoking (any in past 1 month)			0.64		0.42		0.81
Yes	47	0.909		0.732		0.196	
No	76	0.920		0.749		0.187	
Hypertension			0.34		0.24		0.47
Yes	90	0.923		0.743		0.198	
No	33	0.898		0.75		0.171	
Low HDL cholesterol			0.25		0.26		0.79
Yes	8	0.866		0.701		0.209	
No	112	0.921		0.747		0.190	
Family History of Premature CVD			0.55		0.48		
Yes	18	0.899		0.726			0.21
No	105	0.919		0.746		0.145	
						0.200	
High HDL-C			NA		NA		NA
Unknown	3	0.883		0.696		0.171	
No	120	0.917		0.744		0.191	
Diabetes mellitus			0.32		0.36		0.39
Yes	5	0.916		0.787		0.130	
No	118	0.972		0.741		0.194	
Metabolic syndrome							
Abdominal obesity (M≥90cm, F≥80cm)			0.24		0.18		0.52
Yes	72	0.928		0.754		0.200	
No	51	0.900		0.727		0.178	
Triglycerides (≥1.7mmol/L)			0.21		0.17		0.41
Yes	11	0.869		0.699		0.245	
No	111	0.920		0.747		0.189	
Low HDL-C (M≤1.0 and F≤1.3mmol/L)			0.30		0.25		0.65
Yes	7	0.867		0.696		0.163	
No	115	0.919		0.745		0.195	
Fasting glucose (>5.5mmol/L)			0.36		0.37		0.70
Yes	5	0.968		0.786		0.229	
No	117	0.914		0.74		0.192	
Unknown	1	0.953		0.779		0.040	

Table III: Linear regression coefficients of various parameters with CIMT and hs-CRP

	Mean-Max CIMT (mm)				Mean-Mean CIMT (mm)				hs - CRP (mg/dL)			
	Regression Coefficient Estimate	95% Confidence Interval Lower	Upper	p value	Regression Coefficient Estimate	95% Confidence Interval Lower	Upper	p value	Regression Coefficient Estimate	95% Confidence Interval Lower	Upper	p value
Age	0.007173	0.004495	0.009852	<0.0001	0.006306	0.004039	0.008573	<0.0001	0.005198	-0.018155	0.028551	0.6602
Weight	-0.000014	-0.001716	0.001688	0.987	-0.000178	-0.001629	0.001272	0.8082	0.007505	-0.005804	0.020813	0.2665
BMI	0.000618	-0.004927	0.006164	0.826	-0.000077	-0.004806	0.004652	0.9742	0.05927	0.016997	0.101542	0.006
Waist Circumference	0.001372	-0.000902	0.003647	0.235	0.001133	-0.000807	0.003073	0.2499	0.026306	0.008957	0.043654	0.003
TC	0.000725	0.000149	0.001301	0.014	0.000559	0.000065	0.001052	0.0269	0.002116	-0.002512	0.006745	0.3671
LDL-C	0.001016	0.000322	0.001709	0.005	0.000813	0.002190	0.001407	0.0077	0.003154	-0.000246	0.008765	0.2679
HDL-C	-0.001501	-0.003387	0.000386	0.118	-0.001296	-0.002904	0.000312	0.1132	-0.012867	-0.02767	0.001935	0.0878
TG	0.000063	-0.000176	0.000302	0.602	0.000056	-0.000147	0.000260	0.5862	0.001946	0.000101	0.00379	0.039
Glucose	0.001176	-0.000101	0.002452	0.071	0.001084	-0.000001	0.002170	0.0502	0.011276	0.001312	0.021241	0.027
log(hs-CRP)	0.013038	-0.011505	0.035816	0.259	0.011577	-0.007833	0.030988	0.2400				

Table IV: Pearson's correlation of various patient characteristics with CIMT and hs-CRP

	Mean-Max CIMT Correlation		Mean-Mean CIMT Correlation		log hs-CRP	
	Correlation coefficient	p-value	Correlation coefficient	p-value	Correlation coefficient	p-value
Age (years)	0.434	<0.0001	0.448	<0.0001	0.040	0.660
BMI (kg/m2)	0.020	0.826	0.003	0.974	0.245	0.006
Waist circumference (cm)	0.108	0.235	0.105	0.250	0.263	0.003
TC (mmol/L)	0.221	0.014	0.200	0.027	0.082	0.367
LDL-C (mmol/L)	0.255	0.005	0.239	0.008	0.101	0.268
TG (mmol/L)	0.047	0.602	0.050	0.586	0.187	0.039
Glucose (mmol/L)	0.164	0.071	0.177	0.050	0.200	0.003

Table V: Questionnaire assessing awareness and attitudes towards CVD risks and disease

No.	Question	Percentage (%) True	False	Unsure	n Unknown
1	Cardiovascular risk factors are risks that would cause damage or disease to my heart and blood vessels.	90	2	8	6
2	Cardiovascular disease is an important medical condition that I would not ignore.	95	1	4	0
3	The consequent of having cardiovascular disease is that I can end up having stroke or heart attack.	88	1	11	1
4	Some cardiovascular risk factors cannot be modified, treated or controlled such as increasing age, being male and heredity.	51	13	36	0
5	Smokers can reduce their cardiovascular risk factor by quitting the habit.	83	6	11	0
6	Failing to control my high blood pressure/blood sugar/cholesterol will increase my cardiovascular risk.	90	2	8	1
7	Having regular exercise can help reduce my cardiovascular risk.	93	1	6	0
8	Overweight or obese people may reduce their cardiovascular risk by reducing their body weight.	87	2	11	0
9	Now that I know that I have 2 or more cardiovascular risk factors, I am inclined to do something about it, for example modify my diet or lifestyle.	87	0	13	0
10	My source of information about cardiovascular risks comes mainly from the TV/internet/radio/newspapers/magazine.	74	12	14	1
11	My source of information about cardiovascular risks comes mainly from health care professionals i.e., doctors/nurses/ pharmacists.	63	19	18	0
12	I am satisfied with the information available to me about the risks of suffering from cardiovascular diseases.	73	11	16	0

		Percentage (%) Yes	No	n Unknown
13	Did your doctor tell you have a high cholesterol level?	44	56	11

		Percentage (%)
14	As a first step when you were diagnosed with high cholesterol, did the doctor:	
	Only advise you to change your lifestyle eg. Change your diet, stop smoking and/or do more exercise	63
	Only prescribe a tablet?	3
	Both advise lifestyle changes and prescribe a tablet?	27
	Neither advise lifestyle changes nor prescribe a tablet?	7
	Unknown, n =11	
15	I am satisfied with the level of information available to me about high cholesterol.	
	Agree	74
	Disagree	3
	Don't know/not applicable	23
	Unknown, n = 58	
16	Which of the following best describes your current situation?	
	I have not been given a target cholesterol level	20
	I have not reached my target cholesterol level	28
	I'm not sure whether I have reached my target cholesterol level	42
	I have reached my target cholesterol level	10
	Unknown, n= 62	

		Percentage (%) Yes	No	n Unknown
17	In general, how do you feel about the way your high cholesterol has been treated?			
	Satisfied	77	23	79
	Motivated	67	33	93
	Concerned	74	26	84
	Confused	34	66	94
	No strong feelings	37	63	93

		Percentage (%)
18	In general, how often do you see your doctor for a check-up of your cardiovascular risk?	
	About every 6 months	16
	About every year	22
	Less often than once a year	10
	Do not have check ups	47
	Don't know/Can't remember	5
	Unknown, n=62	

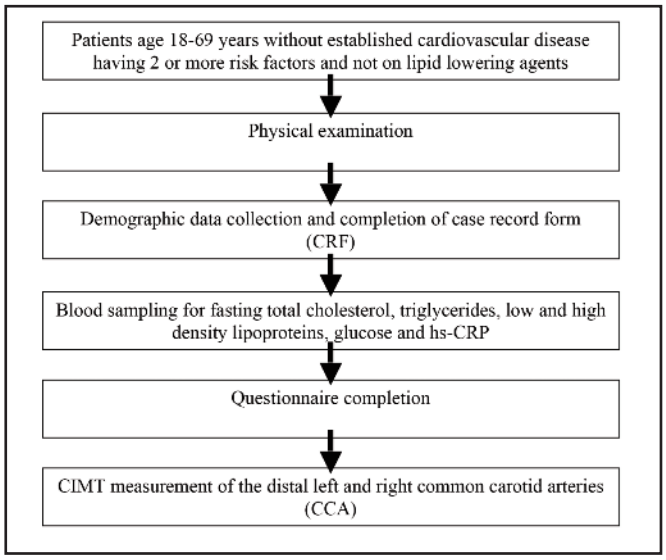

Fig. 1 : Flow chart of study design.

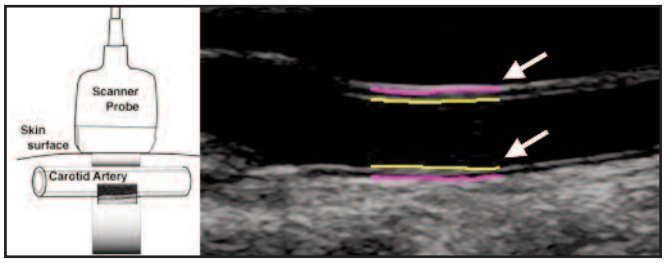

Fig. 2 : Ultrasound scan of the common carotid artery (left) and measurement of CIMT (right, arrows).

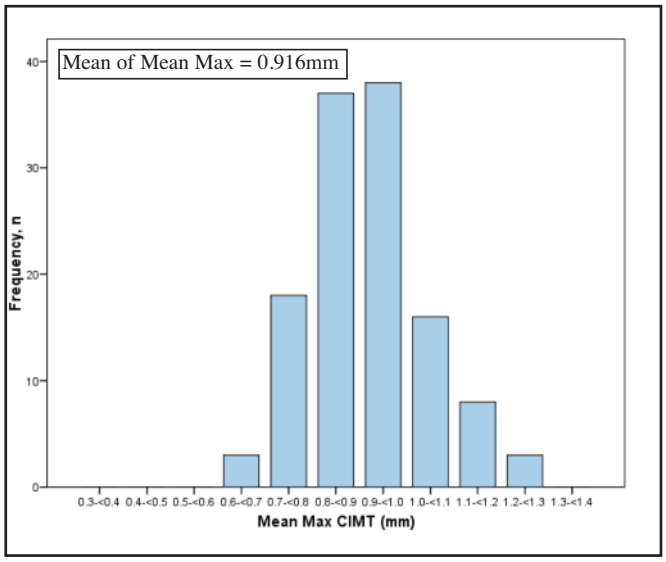

Fig. 3 : Distribution of Mean-Max CIMT.

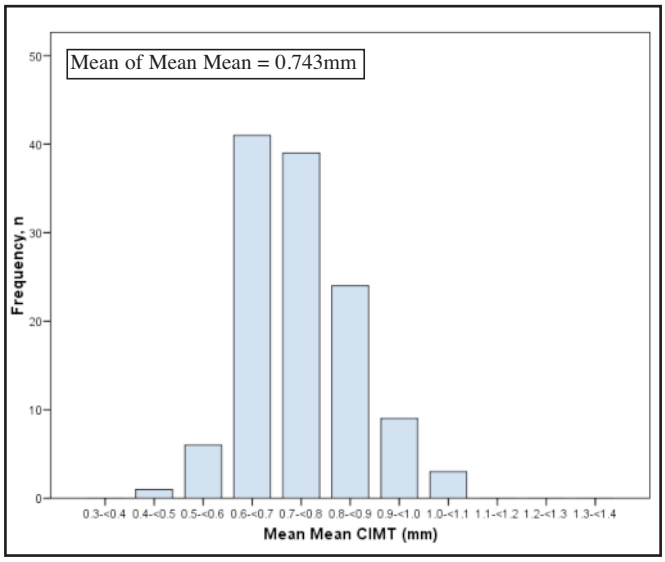

Fig. 4 : Distribution of Mean-Mean CIMT.

There was a significant difference in the ANOVA analysis between both the Mean-Max and the Mean-Mean CIMT and age with p value of <0.0001. The differences in gender, traditional CVD risk factors of BMI, cigarette smoking, hypertension, low HDL-C, family history of premature CVD, diabetes mellitus and metabolic syndrome features such as abdominal obesity, high triglycerides, low HDL-C, impaired fasting glucose were not statistically significant. For the log hs-CRP it was only statistically significant against BMI with a p value of 0.01 and was not for age, traditional risk factors other than BMI nor metabolic syndrome features. These results are shown in Table III. Table 4 revealed that for the CIMT values regardless of the Mean-Max or Mean-Mean measurements had the most positive linear dependence with age with a correlation coefficient of more than 0.4 and a weaker positive linear dependence with total cholesterol and LDL-C of more than 0.2. On the other hand log hs-CRP had statistically significant linear dependence with BMI, waist circumference, triglycerides and fasting glucose levels with a correlation coefficient of around 0.2.

Questionnaire findings

The self administered health questionnaire was conducted successfully having some minor omissions in some answers and deemed not to have significantly altered the results. Generally the questionnaire revealed that our urban population had a an excellent understanding of cardiovascular risk factors and disease above 70% correct in most questions and upwards of 90% of more in 4 questions. About half correctly stated that some risk factors cannot be modified and a third was unsure. The mass media and healthcare staff played the most vital role in spreading health awareness to our study population. Less than half these at risk patients was aware of their absolute cholesterol levels or if they have achieved good control. This could be due to a selection bias on part of the screening nature of this

study. Most surveyed felt satisfied, motivated and concerned at the same time towards how their cholesterol has been managed though nearly half did not have regular check-ups. As mentioned earlier the complete results of the questionnaire are tabulated in Table V.

DISCUSSION

Our study showed that the mean Mean-Max CIMT and Mean-Mean CIMT were 0.916 and 0.743mm respectively for patients with 2 or more CVD risk factors.

As expected, both measurements in the Malaysian population were significantly higher than corresponding values in a normal rural Korean population in the ARIRANG study[13] that documented mean values of up to 0.66mm in men and 0.63mm in women aged 40-70 years. In a previously presented study by the author of this paper, angiographically confirmed CAD patients from a Malaysian cohort with a Syntax Score ranging from 1 to 61 (mean 18) had a Mean-Max CIMT of 0.87mm and 0.81mm in the right and left CCA respectively [22]. Although this study utilised a slightly different methodology with a single maximum measurement along the CCA and having a wide-ranging severity of coronary artery disease, the value was significantly higher than the same rural Korean population and its findings were consistent. A higher plaque burden was found in those with additional cardiovascular risk factors or confirmed CAD.

Interestingly the Mean-Mean CIMT value in the Malaysian cohort was placed second highest after Taiwan among the 8 countries studied. In the main study there was a wide variation across different countries with the overall value being 0.66±0.16mm [21]. In view of the small sample size in this Malaysian population study, care must be taken not to over interpret the significance and correlations of both the Mean-Max and the Mean-Mean CIMT measurements with demographic characteristics and traditional CVD risk factors. Despite this limitation our study demonstrated a statistically significant difference in the ages and CIMT values with a moderate linear correlation ($r > 0.4$) and a weaker but positive linear correlation with total cholesterol and LDL-C. Woo et al had shown that for an age, gender and smoking matched population, healthy Chinese urban dwellers had higher CIMT measurements compared to rural Chinese and that the effects of smoking, HDL-C, and triglycerides on IMT were significantly greater in the urban compared to rural Chinese [23]. Hence, for CIMT to be an effective risk predictor, normal values across different age groups for a given population are needed. The SHAPE guidelines recommended a cut off of >90th percentile instead of an overt plaque of > 50% stenosis in the CCA to classify patients as very high risk for CVD. In the absence of normal values for the Malaysian population this criterion of >90th percentile cannot be applied. Further refinement of cardiovascular risk assessment beyond traditional risk factors will have to depend on identifying an overt carotid plaque, presence and degree of coronary artery calcium, and use of novel biomarkers like hs-CRP.

The hs-CRP levels seen in our study demonstrated a weak but positive linear correlation with features of the metabolic syndrome such as BMI, waist circumference, triglyceride and glucose levels and are in general agreement with the main study. This correlation has been well established in previous studies involving multi ethnic groups [24-27] and it was previously shown that visceral adipose tissue is a source of pro-inflammatory cytokines such as IL-6 which consequently lead to elevated hs-CRP levels [17]. The use of hs-CRP as the sole screening criterion for identifying high risk CVD patients has been confounded by several factors, namely, lack of precision, specificity, level-effect causality of risk of CVD and its relatively higher costs compared to traditional biomarkers such as glucose or lipid profile [28]. The mean hs-CRP level in our study population with 2 or more risk factors was 0.191mg/dL. This was just slightly lower than the threshold for initiating statin for primary prophylaxis in the JUPITER trial with patients having low to moderate risk of CVD [20]. In our study, the mean LDL level was 3.57mmol/L which was sufficiently high to recommend initiating lifestyle intervention and/or statin therapy based on the Adult Treatment Panel (ATP) III guidelines independent of the hs-CRP level for patients with 2 or more risk factors [29].

Overall the health survey revealed a good understanding of the common cardiovascular risk factors and disease. This was probably not unexpected as this was an urban population with easy access to health care information via the mass media and healthcare workers. This finding will encourage primary prevention efforts to be intensively continued at the public healthcare as well as hospital levels. The importance of a focussed approach from relevant government institutions and non-governmental organisations cannot be emphasised enough.

CONCLUSION

Our study successfully defined CIMT levels and hs-CRP levels for those at moderate risk of CVD in a predominantly urban Malaysian population. Measuring these novel CV markers in this population may help us understand how to use them in the local Malaysian context. Defining the best treatment for those at moderate risk of CV disease based on traditional risk assessment remains a challenge due to the heterogenous make-up of the population. Novel CVD risk markers including CIMT and hs-CRP can assist the physician to refine this process. Ultimately, there may not be a single gold standard test. Sound clinical judgement based on an individual's global CV risk may still be the most prudent approach.

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