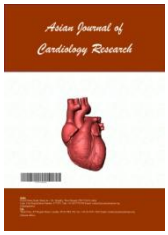

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Carotid Intima-media Thickness as a Non-invasive Predictive Imaging Tool for Occurrence and Severity of Coronary Artery Disease: Correlations with Lipid Profile

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Authors' contributions

This work was carried out in collaboration among all authors. Authors HMM and GA designed the study, performed the statistical analysis and wrote the protocol, Authors HMM and MHH wrote the first draft of the manuscript. Authors HMM, GA and MHH managed the analyses of the study. Authors HMM, GA and MHH managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: It is important to identify patients at risk of developing cardiovascular events to enable preventive interventions and promote lifestyle modifications. Carotid intima–media thickness (CIMT) is an important marker for cardiovascular disease and can be easily measured by a noninvasive test. Increased CIMT has been highly suggested to be associated with coronary artery disease (CAD).
Aim: We aimed to investigate the relationship of CIMT with the presence and extent of significant coronary artery narrowing in patients evaluated by coronary angiography.
Methods: The study was conducted on 100 patients. All of them were subjected to full history taking and clinical examination. Laboratory investigations including: lipid profile [cholesterol,

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triglycerides, LDL-C (low density lipoprotein), HDL-C (high density lipoprotein)], HbA1c (glycated hemoglobin) in diabetics, CRP (C-reactive protein), ECG (electrocardiogram), Echocardiography, carotid Doppler and coronary angiography.

Results: There was a strong positive significant association between abnormal mean IMT and presence of CAD with p value <0.001. We found no significant association between abnormal mean IMT and extent of CAD (number of diseased coronary arteries). Increased CIMT appears to be the most independent factor affect occurrence of coronary artery disease with odds ratio (OR) 5.97 (p value 0.01) followed by CRP level OR 1.50 (p value 0.007), followed by abnormal HDL level OR 1.32 (p value 0.001) and cholesterol level OR 1.02 (p value 0.02).

Conclusions: Thus, the increased CIMT can be used as a predictor of presence of CAD but not of its extent.

Keywords: Atherosclerosis; Carotid Intima Media Thickness (CIMT); Coronary Artery Disease (CAD); coronary angiography; carotid duplex.

1. INTRODUCTION

Cardiovascular disease is one of the leading causes of death in the world and it is clear that atherosclerosis, which is a precursor to coronary artery disease (CAD) and stroke, starts at an early age; therefore the identification of modifiable risk factors for adult cardiovascular disease (CVD) in youth has been a high priority. These risk factors in adults include elevated low-density lipoprotein (LDL), decreased high-density lipoprotein (HDL), elevated blood pressure, diabetes, cigarette smoking and, obesity. Mittelman et al. [1] Guidelines for triage of patients for cardiac catheterization recommend risk assessment and non-invasive testing [2].

The development of ultrasound measurements of carotid intima-media thickness (CIMT) has greatly enhanced the ability to assess subclinical atherosclerosis and to track progression of abnormalities. There are numerous reports on the relationship between carotid artery ultrasound findings and the prevalence of CAD. Most epidemiologic and clinical studies are based on a measurement of the CIMT. Previous studies have shown associations between the CIMT and CAD [3].

Guidelines that support the use of CIMT for the assessment of cardiovascular risk include ACC/AHA guidelines on the initial detection of cardiovascular risk: recommends assessment as class IIA (is reasonable to perform) in individual at intermediate CAD. [4] The main purpose of this study was to find whether there was a relation between CIMT and CAD and whether CIMT could be regarded a marker of presence and extent coronary artery lesions.

2. MATERIALS AND METHODS

2.1 Study Design and Participants

This study included 100 patients with symptoms suggesting CAD attending Qena University Hospital, South Valley University (SVU) in the period from January 2016 to June 2017. The study has been approved by the Ethics Committee of Faculty of medicine, South Valley University, Qena, Egypt and has been conducted in accordance to the Declaration of Helsinki. An informed written consent has been obtained from every included subject.

2.2 Inclusion Criteria

- Patients with symptoms suggesting CAD in whom coronary angiography was indicated with or without diabetes mellitus.
- Age 18 years or more.
- Willing to be included in the study.

2.3 Exclusion Criteria

- Previous myocardial infarction (MI).
- Coronary Artery Bypass Graft (CABG).
- Overt heart failure.
- Cerebrovascular stroke.

2.4 Methodology

We did all the following for all participants: full medical history, clinical examination, lipid profile according to US Preventive Services Task Force (USPSTF) cholesterol guidelines [5] target level of total cholesterol <200 mg/dl, LDL <100 mg/dl, HDL ≥ 60 mg/dl, triglycerides (TGs) < 150 mg/dl; Glycated hemoglobin (HbA1c) for diabetic patients; the 2016 American Diabetes Association Standards of Medical Care in

Diabetes added the HbA1c ≥ 48 mmol/mol (≥6.5 diabetes control and complications trial (DCCT) %) [6] as another criterion for the diagnosis of diabetes); C-reactive protein: Cut points of risk are: Low: <1.0 mg/dL; average: 1.0–3.0 mg/dL; high: >3.0 mg/dL, [7] 12 leads Electrocardiography (ECG) and echocardiography.

Carotid Duplex Ultrasonography, B-mode ultrasound of the carotid arteries was performed using a high frequency (7.5 MHz) linear transducer; extracranial carotid arteries has been scanned bilaterally along the anterior, lateral and posterior axes, in transverse and longitudinal planes. Patients lying in supine position with the neck in mild hyperextension position as well as almost 45 degrees rotation away from the examined side; measurements had been made on frozen images, 1 cm below the carotid bifurcation, at the end of diastole. On the screen displaying the frozen image, 2 cursors positioned on the boundaries of the intima and media respectively. The distance between the cursors was recorded to the nearest 0.1 mm. IMT of the common carotid arteries considered as the distance between the lumen-intima interface and the leading edge of media adventitia interface. Thus, only the intima which appears as echogenic layer and the media which appears as echo-poor layer were included in the measurement. [8] A single experienced observer performed IMT measurements. Intima-media thickness values of more than 0.9 mm (ESC) or over the 75th percentile) should be considered abnormal [9].

Coronary angiography: Angiographic evaluations of coronary arteries performed to CAD patients by percutaneous technique via transfemoral access. One-vessel disease was defined as the presence of a lumen diameter reduction greater than 50% in one major coronary artery. Two-vessel disease was defined as the presence of a lumen diameter reduction greater than 50% in two major coronary arteries. Three vessel disease was defined as the presence of a lumen diameter reduction greater than 50% in three major coronary arteries. The extent of CAD was coded as 1, 2 or 3 according the number of major coronary vessels with luminal stenosis > 50% [10].

2.5 Statistical Analysis

Data was analyzed using STATA intercooled version 14.2. Quantitative data was represented as mean, standard deviation, median and range. Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. Sensitivity, specificity, positive predicted value and negative predictive value were calculated. Univariate and multivariate logistic regression analyses were done to detect the factors affecting occurrence of CAD. P value was considered significant if it was less than 0.05.

3. RESULTS

A total of 100 patients were enrolled. There were 58 males and 42 females. The mean age was 55.17±9.79 years. 59 patients (59%) were diabetic with HbA1c 8.31%±1.14; 54 patients (54%) were hypertensive while 35 patients (35%) were smokers. A little more than half of the cases (55 patients; 55%) had a history of CVD.

Out of our study 65% of patients had CAD; 20% of patients had single vessel disease, 28% of them had two vessel disease and 17% had three vessel disease. 35 patients (35%) had abnormal CIMT (>0.9 mm) while 65 patients (65%) had normal CIMT (≤0.9).

There was positive significant associations between abnormal mean CIMT and abnormal serum cholesterol level with p value <0.0001, abnormal serum LDL level (p value <0.007), abnormal serum HDL level (p value 0.02), and abnormal serum CRP level (high risk) (p value 0.01). We found no significant association between abnormal mean CIMT and either age, gender, smoking, diabetes mellitus, hypertension or triglyceride level (Table 1).

There was a strong positive significant association between abnormal mean CIMT and the presence of CAD with p value <0.001 but no significant association with the extent of CAD (number of diseased coronary arteries) was detected (Table1, Fig.1).

Using the multivariate logistic regression analysis for the possible risk factors for the occurrence of CAD, we found a significant increased risk with increased CIMT (Odd's ratio "OR" = 5.97), high CRP level (OR = 2.50), abnormal HDL level (OR = 1.32) and abnormal cholesterol level (OR = 1.02); respectively (Table 2).

Using the Receiver operating Characteristics (ROC) curve analysis, we observed that the sensitivity of increased CIMT as a predictor to

the presence of CAD reached 46.15% with a high specificity of 85.71%. The area under the ROC curve (AUC) was 0.66 with and overall accuracy of 65.93% (Fig. 2).

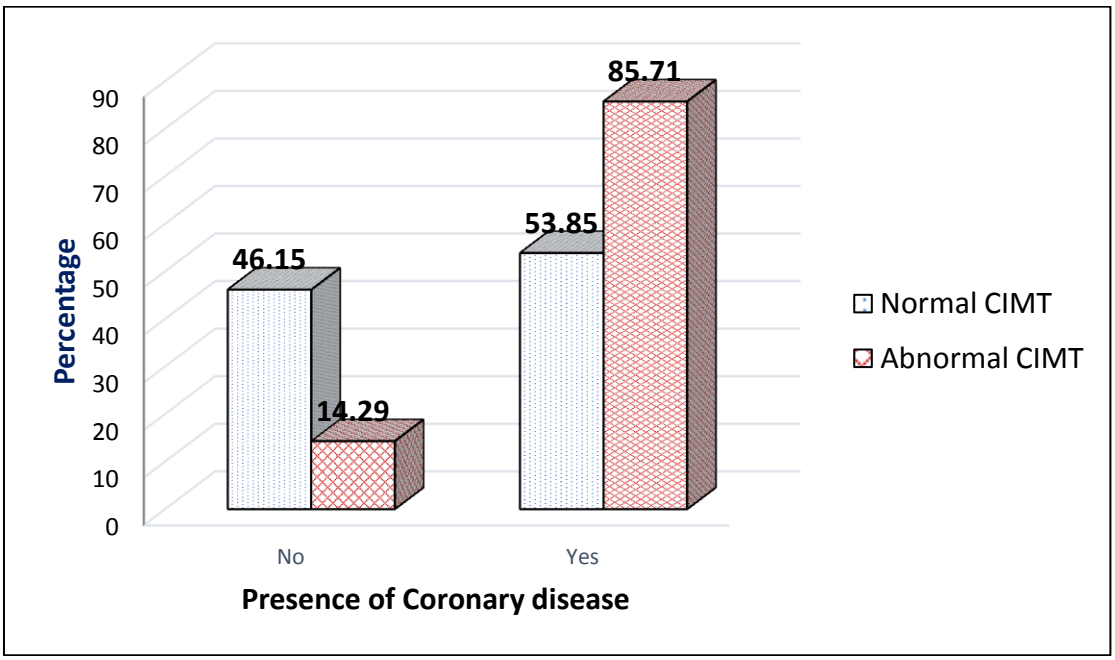
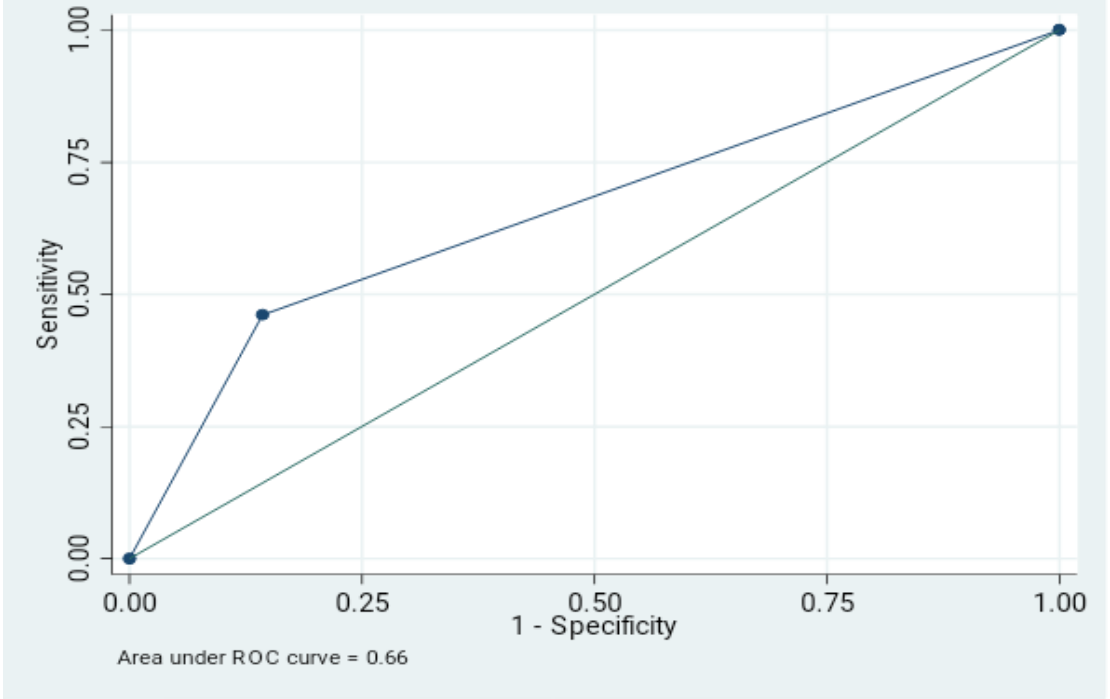


Fig. 1. Comparison between normal and abnormal CIMT according to presence of Coronary disease



AUC	Sensitivity%	Specificity%	PPV %	NPV%	Accuracy %
0.66 (0.57-0.74)	46.15	85.71	85.71	46.15	65.93

Fig. 2. Receiver Operating Characteristic (ROC) curves for the utility of CIMT in screening for CAD

Table 1. Comparison between patients with normal vs those with abnormal CIMT

Variables	Normal CIMT N=65	Abnormal CIMT N=35	P value
Age/years			
<50	23 (35.38%)	8 (22.86%)	0.43
50-60	24 (36.92%)	15 (42.86%)	
>60	18 (27.69%)	12 (34.29%)	
Gender			
Females	27 (41.54%)	15 (42.86%)	0.90
Males	38 (58.46%)	20 (57.14%)	
Smoking			
No	42 (64.62%)	23 (65.71%)	0.91
Yes	23 (35.38%)	12 (34.29%)	
DM			
No	27 (41.54%)	14 (40.00%)	0.88
Yes	38 (58.46%)	21 (60.00%)	
Hypertension			
No	32 (49.23%)	14 (40.00%)	0.38
Yes	33 (50.77%)	21 (60.00%)	
Cholesterol			
Normal	27 (41.54%)	2 (5.71%)	<0.0001
Abnormal	38 (58.46%)	33 (94.29%)	
Triglyceride			
Normal	32 (49.23%)	13 (37.14%)	0.25
Abnormal	33 (50.77%)	22 (62.86%)	
LDL			
Normal	11 (16.92%)	0	0.007
Abnormal	54 (83.08%)	35 (100%)	
HDL			
Normal	13 (20.00%)	1 (2.86%)	0.02
Abnormal	52 (80.00%)	34 (97.14%)	
CRP			
Low risk	9 (13.85%)	0	0.01
Average risk	18 (27.69%)	5 (14.29%)	
High risk	38 (58.46%)	30 (85.71%)	
Presence of Coronary disease			
No	30 (46.15%)	5 (14.29%)	0.001
Yes	35 (53.85%)	30 (85.71%)	
Number of vessels affected if present			
1	13 (37.14%)	7 (23.33%)	0.44
2	13 (37.14%)	15 (50.00%)	
3	9 (25.71%)	8 (26.67%)	

Table 2. Factors affecting occurrence of coronary disease among the included patients

Variables	Multivariate odds ratio (95% confidence interval)	P value
Cholesterol	1.02 (1.004-1.06)	0.02
HDL	1.32 (1.12-1.54)	0.001
CRP	2.50 (1.28-4.86)	0.007
CIMT>0.9	5.97 (1.52-23.44)	0.01

4. DISCUSSION

Atherosclerosis is a systemic disease, and carotid and coronary arteries are the two most common sites that are involved in atherosclerosis. Increased CIMT may not only be a surrogate marker of subclinical atherosclerosis but also be an indicator of presence of coronary atherosclerosis [10].

The current study showed that there was strong positive significant association between

abnormal mean CIMT and presence of CAD with p value <0.001 but no significant association with the extent of CAD (number of diseased coronary arteries) was observed. These findings were consistent with those of study of Wani, et al. [10] an Indian cross-sectional study conducted from March 2013 to September 2015 on a total of 100 patients admitted to for undergoing coronary angiography indicating for suspected coronary artery disease. The risk factors evaluated in this study included age, body mass index, sex, dyslipidemia, hypertension, diabetes mellitus and smoking. CAD was assessed and classified by coronary angiography and CIMT was assessed by carotid doppler. They found that there was a positive relationship between CIMT and CAD. Many previous studies with similar results were performed [11]. In contrast with results of our study, Wani, et al. [10] proved that CIMT can predict the extent of CAD.

In our study, logistic regression analysis of factors affecting occurrence of CAD shows that increased CIMT appears to be the most independent factor affecting occurrence of CAD with OR = 5.97 (p value = 0.01). This was in agreement with previous studies [12,13]. It was followed by CRP level (OR = 1.50; p value = 0.007) consistently with results of Hoefer et al, [14] then abnormal HDL level (OR = 1.32; p value = 0.001) and cholesterol level (OR = 1.02; p value = 0.02) as previously reported by Wang, et al. [15].

In the present study, increased CIMT has a sensitivity, specificity, positive and negative predictive values of 46.15%, 85.71% and 85.71%, 46.15% respectively. These results suggested that the presence of carotid atherosclerosis as detected by carotid duplex could be considered as a marker of presence of CAD, and may be used to define the need for angiography. A previous study [16] also concluded that CIMT as a measure of Coronary Artery Stenosis (CAS) had better positive predictive value (PPV) for CAD. Another study showed that sensitivity, specificity, positive and negative predictive values of CIMT for CAD were 81.3%; 81.8%; 94.9% and 51.5%; respectively [17].

In our study the diagnostic accuracy of CIMT was 65.93 %, AUC 0.66; with 95% confidence interval of (0.57-0.74). These findings are similar to those of a prospective study including 300 patients with suspected stable CAD, admitted for an elective coronary angiography and carotid ultrasound, which showed a modest predictive accuracy for CAD (0.638) with 95% confidence interval of (0.576-0.701) [12].

In this study there was positive significant association between abnormal mean CIMT and abnormal serum cholesterol level with p value <0.0001), abnormal serum LDL level (p value <0.007), abnormal serum HDL level (p value = 0.02) and abnormal serum CRP level (p value = 0.01). Previous studies reported a significant correlation between dyslipidemia and carotid atherosclerosis with increased cardiovascular risk. [15] Further more an investigation carried out in 2015 showed that the CRP has emerged as an interesting novel and potentially clinically useful marker for atherosclerosis and increased cardiovascular risk [14].

We observed no significant association between abnormal mean CIMT and either age, gender, smoking, DM, hypertension or TGs. These finding were at a variance with those of Wani et al. [10] who stated that risk factors like age, smoking, BMI, cholesterol, hypertension, and diabetes had significant positive effect on CIMT; whereas gender, VLDL, TGs, HDL and LDL were statistically insignificant in affecting CIMT.

5. CONCLUSION

Our study concluded that, in addition to the traditional risk factors of CAD, there are other non-traditional risk factors that significantly associated with atherosclerosis such as CRP and carotid atherosclerosis. The evaluation of Doppler ultrasound of carotid arteries might provide the clinician with additional information about the global cardiovascular risk of the patients. The mean CIMT showed good positive predictive value for the presence of coronary artery lesions. Large prospective studies are further required to establish the link between these parameters and the complexity of CAD.

CONSENT

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with Ethics committee of the Faculty of Medicine, South Valley University, Qena, Egypt and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. An informed written consent has been obtained from every included patient Ethics committee's reference number: 12/2015.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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