

## Relation Between Carotid Artery Plaque Score and Severity of Coronary Artery Disease in Patients with Metabolic Syndrome

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### ABSTRACT

**Background:** Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as diabetes, fatty liver and several cancers.

**Objectives:** To assess the relationship between carotid plaque score by carotid ultrasonography and severity of coronary artery disease (CAD) by SYNTAX score in metabolic syndrome patients undergoing coronary angiography.

**Patients and Methods:** A cross sectional case-control study included 100 persons divided into two groups: Group (1) included 50 patients with metabolic syndrome and group (2) that included 50 patients did not fulfill the criteria for metabolic syndrome. They were selected from those attending the Catheterization Unit of the Cardiology Department, Al-Azhar University Hospital, Assiut.

**Results:** There was no statistically significant difference between the two groups regarding age and gender ( $P > 0.05$ ). There were a highly statistically significant difference between the two groups regarding hypertension, diabetes mellitus and waist circumference ( $P < 0.0001$ ). Regarding HDL level, there was a statistically significant difference ( $P = 0.030$ ), while there was no statistically significant difference regarding triglycerides level ( $P = 0.159$ ). There was highly statistically significant difference between the two groups regarding plaque score and SYNTAX score ( $P < 0.0001$ ) with strong correlation ( $r=0.907$ ). There was a moderate positive correlation between plaque score and number of risk factors for metabolic syndrome ( $r=0.5$ ) with a very high statistically significant level ( $P < 0.0001$ ).

**Conclusion:** There was a moderate correlation between carotid artery plaque score and Syntax score in metabolic syndrome patients.

**Keywords:** Metabolic syndrome, Carotid artery Plaque score, SYNTAX score, Atherosclerosis.

### INTRODUCTION

Metabolic syndrome (MetS) is the commonly used term for a cluster of clinical and metabolic factors that increase the risk for type 2 diabetes mellitus (T2DM), coronary artery disease (CAD) and stroke. The interrelated risk factors include central obesity, dyslipidemias, hypertension, hypercoagulable state and insulin resistance<sup>(1)</sup>.

Over years, several groups and organizations tried to find accepted diagnostic criteria of metabolic syndrome. The World Health Organization (WHO) created the first internationally recognized definition of MetS in 1998, which was modified by the European Group for the Study of Insulin Resistance (EGSIR) in 1999. In 2001, the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP111) updated the guidelines for MetS, and in 2003, the American Association of Clinical Endocrinologists (AACE) proposed their definition<sup>(2)</sup>.

In 2005, the International Diabetes Federation (IDF) provided the consensus worldwide definition of MetS<sup>(3)</sup>. This definition includes waist circumference as a prerequisite for the identification of MetS while also comprising a number of the common features of the AACE, WHO, and EGSIR definitions, namely, measurement of triglycerides (TG) and of high-density lipoprotein (HDL)-cholesterol and evaluation of fasting

glucose and blood pressure<sup>(4)</sup>. The cut-off limits of waist circumference are specific to the gender and ethnic groups in the IDF criteria<sup>(3)</sup>.

The term "atherosclerosis" describes the association of fatty degeneration and vessel stiffening. This process affects medium and large-sized arteries and is characterized by patchy intramural thickening of the subintima that encroaches on the arterial lumen. Each vascular bed may be affected by this process. The etiology, treatment and clinical impact of atherosclerosis varies from one vascular bed to another. The earliest visible lesion of atherosclerosis is the fatty streak, which is due to an accumulation of lipid-laden foam cells in the intimal layer of the artery. With time, the fatty streak evolves into a fibrous plaque, the hallmark of established atherosclerosis. Ultimately the lesion may evolve to contain large amounts of lipid; if it becomes unstable, denudation of overlying endothelium or plaque rupture may result in thrombotic occlusion of the overlying artery<sup>(5)</sup>.

Carotid artery intima-media thickness (CIMT) has been reported as representative of subclinical and asymptomatic atherosclerotic vascular diseases, shown in several large ultrasonographic measurement of IMT, and therefore a procedure to detect primordial atherosclerosis. The amount of lesion in the common



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carotid artery (CCA) has been reported to correlate to the extent of atherosclerotic lesions elsewhere in the body. Over more than two decades, CIMT has been extensively researched and explored for its medical and clinical viability, and available in clinically since 2002. Several large, research-based cohort studies have clearly indicated a relationship between CIMT and CV events and emphasized its use. Evaluating for the presence or absence of plaque in conjunction with measuring common carotid artery intima-media thickness (CIMT) offers a better representation of subclinical vascular disease and CVD risk than only measuring CIMT <sup>(6)</sup>.

The syntax score (SX score) is one of coronary scoring systems that is used by cardiologists and cardiac surgeons to grade the complexity of CAD. The functional impact of coronary circulation with all its anatomical components including the presence of bifurcations, total occlusions, thrombus, calcification and small vessels must be taken into account. It was designed to predict the risk of percutaneous and surgical revascularization <sup>(7)</sup>.

#### AIM OF THE STUDY

This study aimed to assess the relationship between carotid plaque score by carotid ultrasonography and severity of CAD by SYNTAX score in metabolic syndrome patients undergoing coronary angiography.

#### PATIENTS AND METHODS

Patients were selected from those attending the Catheterization Unit of the Cardiology Department, Al-Azhar University Hospital, Assiut, Egypt.

This study comprised 50 metabolic syndrome patients (mean age  $62.24 \pm 6.08$  years, 33 females and 17 males) and 50 apparently healthy age- and sex-matched controls (mean age  $59.88 \pm 6.53$  years, 32 females and 16 males).

**Inclusion Criteria:** Patients who underwent coronary angiography and accepted being tested by ultrasound to measure carotid atherosclerosis were randomly selected and recruited.

**Exclusion Criteria:** Hemodynamically unstable patient or patients with end stage liver or renal disease, or patient with acute coronary syndrome.

**All patients in this study were subjected to the following:**

- 1- **Full history:** taken from all patients, including name, age, sex, smoking, alcohol, hypertension, diabetes mellitus, cerebro-vascular stroke, medications, cardiac history, peripheral artery disease and family history.
- 2- **Full clinical examination:** with special emphasis on the following data:
  - Pulse: rate and rhythm.
  - Blood pressure.
  - Head and neck examination.
  - Upper and lower limb examination.

- Chest and heart examination.
  - BMI measurement.
- 3- **Laboratory investigations:** including lipid profile, kidney function tests, complete blood count, INR, Blood glucose level.
  - 4- **Twelve-lead surface ECG:** (Fukuda ECG machine, Japan) to assess ECG changes suggestive of ischemia.
  - 5- **Resting echocardiography:** A Vivid S5 N phased array system equipped were used. (Made in GE Healthcare, Horten, Norway). Complete Transthoracic Echocardiographic examination according to American Society of Echocardiography (ASE) including conventional echocardiography. All echocardiographic examinations performed after 20–30 min of rest with the patient in quiet respiration in the partial left lateral decubitus position, using a 2–4 MHz transducer and accompanied by recording resting electrocardiography for assessment of left ventricular functions and possible resting wall motion abnormalities <sup>(8)</sup>.
  - 6- **Carotid U/S:** A high-resolution B mode, color Doppler and pulse Doppler ultrasonography of both carotid arteries using Siemens Acson x300 machine (Germany). Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe will be rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of media-adventitia echo. At least three measurements will be taken over 1-cm length of far wall of each CCA segment. The measurements of both sides were averaged to obtain the mean IMT. When plaque was present in the segment used for measuring the mean IMT, the plaque thickness was averaged into the mean IMT measurement. Focal intima-media thickening  $\geq 1.5$  mm specified the presence of a plaque. The PS was calculated by summing up the thickness of all plaques located in both carotid arteries <sup>(9)</sup>.
  - 7- **Coronary angiography:** Coronary angiography was performed using Philips machine (USA) under local anesthesia using seldinger technique. The procedure is sterile, and all potential access sites must be disinfected <sup>(10)</sup>.
    - **Pre medication:** Sedation, anti-allergic, antiemetic
    - **Contrast media:** Xenetix 300mg/ml (Iobitridol). Maximum amount =  $5(\text{body weight})/\text{Sr. Creatinine}$ .
    - **Catheters:** Judkins (J) & William (W) JL 3.5 & JL 4, JR 3.5 & JR 4
    - **Approaches:** Percutaneous techniques usually from femoral artery was used.
    - **Projections:** Selective left and right coronary angiograms performed in multiple angulated views: AP (anteroposterior) cranial & caudal. LAO (Left Anterior Oblique) cranial & caudal. RAO cranial & caudal. Lateral view.

**Ethical considerations:**

This study was approved by the Ethical Committee of the Faculty of Medicine Al-Azhar University, Assuit. Written informed consent was obtained from each patient.

**Statistical methods**

Data obtained from the present study were computed using SPSS version 20 under the platform of

Microsoft Windows 10, Professional Edition. Continuous data were expressed in the form of Mean ± SD. While categorical data were expressed in the form of count and percent. A comparison of continuous data was performed utilizing Student's tests (t), while categorical data were done using Chi-square (X2) test. The non-significant difference if P > 0.05. The significant difference if P ≤ 0.05. The highly significant difference if P < 0.001.

**RESULTS**

**Table (1):** Comparison between studied groups regarding age, and gender

	<b>Group I (Metabolic syndrome)</b>	<b>Group II (Non-metabolic syndrome)</b>	<b>P-value</b>
<b>Age (Years):</b>			
<b>Mean ± SD</b>	62.24 ± 6.08	59.88 ± 6.53	0.064
<b>Gender: n (%)</b>			
<b>Males</b>	17 (34)	18 (36)	0.834
<b>Females</b>	33 (66)	32(64)	

There was no statistically significant difference between the two groups regarding age, and gender (P > 0.05 for each).

**Table (2):** Comparison between the two groups regarding risk factors for metabolic syndrome

	<b>Group I (Metabolic syndrome)</b>	<b>Group II (Non-metabolic syndrome)</b>	<b>P-value</b>
<b>Mean ± SD</b>			
<b>TG (mg/dl)</b>	170.26 ± 12.25	166.06 ± 16.92	0.159
<b>HDL (mg/dl)</b>	42.52 ± 5.63	45.02 ± 5.72	0.030
<b>WC (cm)</b>	87.48 ± 7.59	81.60 ± 7.96	<0.0001
<b>n (%)</b>			
<b>HTN</b>	40 (80)	15 (30)	<0.0001
<b>DM</b>	34 (68)	5 (10)	<0.0001

TG = triglycerides. HDL = High-density lipoprotein. WC = Waist circumference. HTN = Hypertension. DM = Diabetes Mellitus. n = number

The mean triglycerides level of group one was 170.26 ± 12.25 while the mean triglycerides level of group two was 166.06 ± 16.92. There was no statistically significant difference between the two groups regarding triglycerides level (P-value 0.159). The mean HDL level of group one 42.52 ± 5.63 while the mean HDL level of group two was 45.02 ± 5.72. There was statistically significant difference between the two groups regarding HDL level (P-value 0.030). The mean waist circumference of group one was 87.48 ± 7.59 while the mean waist circumference of group two was 81.60 ± 7.96. There was very high statistically significant difference between the two groups regarding waist circumference (P-value < 0.0001). There was very high statistically significant difference between the two groups regarding hypertension (P-value < 0.0001). There was very high statistically significant difference between the two groups regarding DM (P-value < 0.0001) as shown in table (2).

**Table (3):** Comparison between the two groups regarding plaque score

	<b>Group I (Metabolic syndrome)</b>	<b>Group II (Non-metabolic syndrome)</b>	<b>P-value</b>
<b>Plaque score</b>			
<b>Mean ± SD</b>	3.44 ± 1.60	1.16 ± 1.43	< 0.0001

SD= Standard Deviation

The mean plaque score of group one was 3.44 ± 1.60, while the mean plaque score of group two was 1.16 ± 1.43. There was very high statistically significant difference between the two groups regarding plaque score (P < 0.0001) as shown in table (3).

**Table (4):** Comparison between the two groups regarding Syntax score

	<b>Group I (Metabolic syndrome)</b>	<b>Group II (Non-metabolic syndrome)</b>	<b>P-value</b>
<b>Syntax score</b>			
<b>Mean ± SD</b>	34.2000 ± 14.846	20.3600 ± 12.386	< 0.0001

SD= Standard Deviation

The mean SYNTAX score of group one was 34.2000 ± 14.846 while the mean SYNTAX score of group two was 20.3600 ± 12.386. There was very high statistically significant difference between the two groups regarding SYNTAX score (P < 0.0001) as shown in table (4).

**Table (5):** Comparison between plaque score in hypertensive and non-hypertensive patients

	<b>HTN</b>	<b>Non-HTN</b>	<b>P-value</b>
<b>Plaque score</b>			
<b>Mean ± SD</b>	2.7091 ± 1.84	1.8000 ± 1.872	0.017
<b>Number of patients (%)</b>			
<b>Male</b>	55 (55)	45 (45)	

HTN= Hypertensive. Non-HTN= Non-hypertensive. SD= Standard deviation.

The mean plaque score of HTN patients was 2.7091 ± 1.84, while the mean plaque score of non-HTN patients was 1.8000 ± 1.872. There was a statistically significant difference between the two groups regarding plaque score (P-value 0.017), as shown in table (5).

**Table (6):** Comparison between plaque score in diabetic and non-diabetic patients

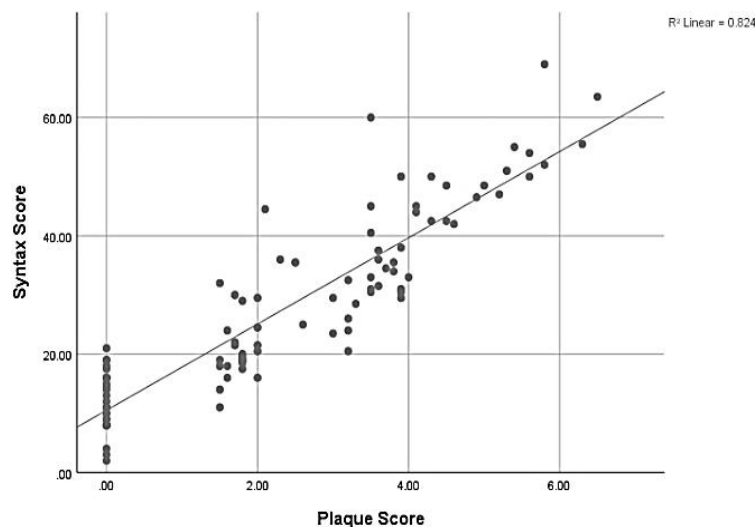
	<b>Diabetics</b>	<b>Non-diabetics</b>	<b>P-value</b>
<b>Plaque score</b>			
<b>Mean ± SD</b>	3.4077 ± 1.599	1.5918 ± 1.744	< 0.0001
<b>Number of patients (%)</b>			
<b>Male</b>	39 (39)	61 (61)	

SD= Standard deviation

The mean plaque score of diabetic patients was 3.4077 ± 1.599, while the mean plaque score of non-diabetic patients was 1.5918 ± 1.744. There was a very high statistically significant difference between the two groups regarding plaque score (P-value < 0.0001) as shown in table (6).

**Correlation between Plaque score and SYNTAX score**

There was a strong correlation between plaque score and SYNTAX score (r=0.907) with a very high statistically significant level (P-value is < 0.0001) as shown in figure (1).



**Figure (1):** Correlation between Plaque score and Syntax score.

### Correlation between plaque score and number or risk factors for metabolic syndrome

There was a moderate positive correlation between plaque score and number of risk factors for metabolic syndrome ( $r = 0.5$ ) with a very high statistically significant level (P-value is  $< 0.0001$ ) as shown in figure (2).

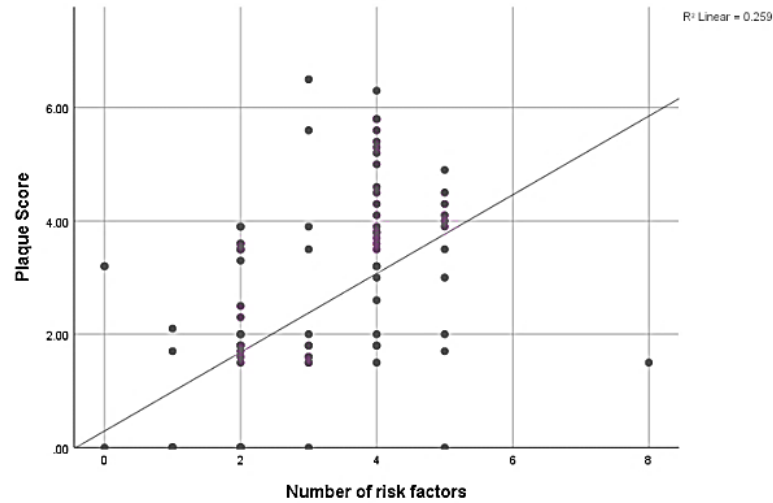


Figure (2): Correlation between Plaque score and Syntax score.

### Correlation between plaque score and number or risk factors for metabolic syndrome

There was a weak correlation between plaque score and waist circumference ( $r = 0.179$ ) with a non-statistically significant level (P-value is  $< 0.074$ ).

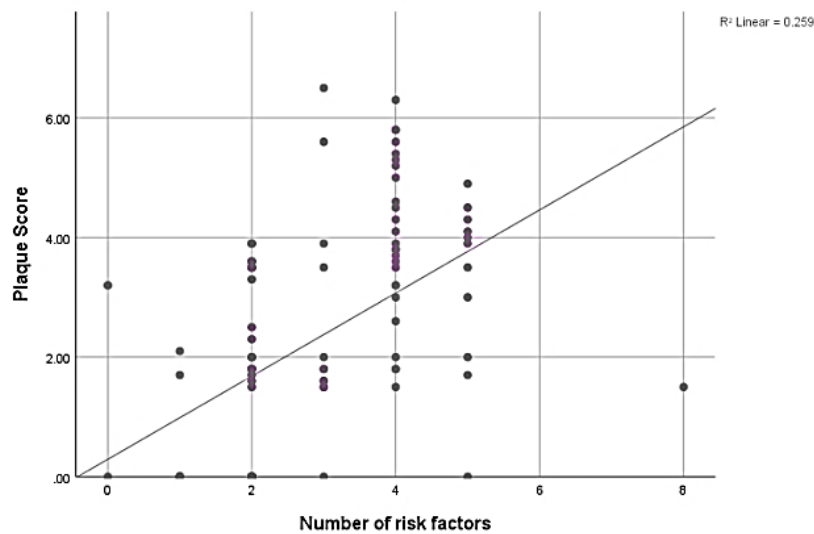


Figure (3): Correlation between plaque score and number or risk factors for metabolic syndrome.

### Correlation between plaque score and number or risk factors for metabolic syndrome.

There was a moderate positive correlation between plaque score and number of risk factors for metabolic syndrome ( $r = 0.5$ ) with a very high statistically significant level (P-value  $< 0.0001$ ) as shown in figure (3).

### DISCUSSION

In our study, we did not find statistically significant difference between the gender of participants and plaque score. This disagrees with Kawada *et al.*<sup>(11)</sup> who found that there was positive correlation between male gender and plaque score. In addition, Iglseder *et al.*<sup>(12)</sup> found

that IMT and plaque score were only significantly correlated in female patients with metabolic syndrome after adjustment for the other risk factors.

In our study, we found that there was a positive correlation between hypertension and plaque score. Our finding comes in agreement with other researcher's findings. To investigate which of blood pressure indices could correlate with carotid atherosclerosis and plaque score, Cheng *et al.*<sup>(13)</sup> found that both central and peripheral blood pressure indices were correlated with carotid atherosclerosis, however, the association between central pressure indices and plaque presence were stronger than those of brachial pressures. To investigate whether systolic or diastolic blood pressure

could correlate with plaque score, **Alizargar and Bai** <sup>(15)</sup> and **Chi et al.** <sup>(16)</sup> found that systolic blood pressure is associated with carotid atherosclerosis and plaque score and not diastolic blood pressure. Blood pressure variability is well known to affect the progression of carotid plaques, **Kolyviras et al.** <sup>(14)</sup> investigated the blood pressure variability by 24-hour ambulatory blood pressure monitoring and found that diastolic time rate is associated with carotid atherosclerosis and plaque score and not systolic time rate.

We found a very high statistically significant difference between the plaque score of diabetic patients versus non-diabetics (P-value < 0.0001). Our findings come in agreement with other investigator's findings like **Sturlaugsdottir et al.** <sup>(17)</sup> who conducted a study on 6524 patients and found that participants with T2DM had greater plaque prevalence, 2-fold higher in those < 50 years and 17-30% greater in age groups 50-54 to 60-64. Moderate or severe significant difference in prevalence was 24% in age group 50-54 and  $\geq 60\%$  in older age groups compared to non-T2DM. In addition, **Bartman et al.** <sup>(18)</sup> found that plaque score is predictive of microvascular complications in patients with type 2 diabetes mellitus. In contrast, **Mitsubishi et al.** <sup>(19)</sup> found no difference regarding plaque score in Japanese participants with type 2 diabetes versus non-diabetics.

Our study found that plaque score (PS) is higher in metabolic syndrome group than non-metabolic group and there was moderate positive correlation between plaque score and number of components of metabolic syndrome. Moreover, there was a strong positive correlation between plaque score and Syntax score, which was used as indicator for severity of coronary artery disease. In a cross-sectional study from the multiethnic Northern Manhattan Study, MetS and the number of MetS components was significantly associated with plaque presence. Furthermore, there was a significant association between MetS and arterial stiffness, independent of the presence of carotid plaque and IMT and persons with MetS had higher rates of progression of carotid atherosclerosis, measured as formation of new plaques and carotid stenosis. From these reports, relationship between MetS and carotid atherosclerosis should be explored by a follow-up study <sup>(20, 21)</sup>. This is concordant with many studies, which have also shown that plaque score is an important predictor of CAD. **Morito et al.** <sup>(22)</sup> found that PS was more closely represented the atherosclerotic status of the carotid artery than the IMT. They also found that subjects with carotid plaques in their study group had a higher risk of heart attack. This indicated that the presence of carotid plaques is an independent predictor for the presence and severity of CAD.

Meta-analysis by **Terzi et al.** <sup>(23)</sup>, showed a significantly higher diagnostic accuracy when PS predicted future myocardial infarction compared to CIMT. Also **Sakaguchi et al.** <sup>(24)</sup> studied the relationship

between coronary angiographic findings and CIMT and PS. They concluded that both were indicators for the presence of CAD. Thus, the addition of carotid plaque measurements may extend the information regarding the status of coronary atherosclerosis. We therefore investigated the relationship between carotid IMT, PS and coronary artery lesions, given the complexity of lesions, we used SX score as an independent risk factor for coronary artery multi-vessel disease in patients with carotid atherosclerosis. The results suggest that the carotid plaque is more closely associated to coronary artery atherosclerosis and PS is an independent predictor of the presence of CAD, but the mean IMT was not. Thus, PS values were better indicators than IMT for predicting the severity as well as the presence of CAD. Taken together, although the larger IMT is an important indicator of the early stages of atherosclerotic lesions and is a simple test method to assess the presence of CAD.

Our results showed that higher PS values are more useful than IMT to predict the severity of CAD <sup>(24)</sup>. In addition, the PS presented independent predictive value for the presence of coronary artery disease and complex coronary artery disease, but the mean IMT did not. A wider range observation of the carotid arteries than that for the mean IMT is required to obtain PS. Therefore, the PS value may represent the atherosclerotic condition of the carotid artery more precisely than the mean IMT value. This may explain the superiority of the PS in predicting the status of coronary artery disease. This is also concordant with **Kawada et al.** <sup>(11)</sup>, who found that there was a trend between the number of components of metabolic syndrome and carotid atherosclerosis and plaque score.

Our study found that SYNTAX score was higher in metabolic syndrome group than non-metabolic group. Similar to our results, **Solymoss et al.** <sup>(25)</sup> showed that MetS was significantly related to more severe coronary artery disease by SYNTAX and angiographic alterations and higher frequencies of unstable angina, myocardial infarction, PCI, and CABG. Another important finding in their study was the 1.5 to 3-fold increased risk of new onset CVD in patients with MetS without diabetes. Our results are in concordance with a study performed by **Miri et al.** <sup>(26)</sup>, which showed a significant relationship between MetS and CAD severity according to angiography documents by SYNTAX score in Iranian subjects. In addition, we showed that presence of diabetes had significant effect on the CAD severity among subjects with MetS.

## CONCLUSION

Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as diabetes, fatty liver, and several cancers.



- There was a moderate correlation between carotid artery plaque score and Syntax score in metabolic syndrome patients.
- Detection of carotid artery plaques and calculation of plaque score may help to predict the severity and complexity of coronary artery affection in metabolic syndrome patients.
- Hypertension and diabetes mellitus are the most important risk factors for development of carotid artery plaques in metabolic syndrome patients.

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