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Can Metric Parameter Combining Metabolic Syndrome Components Usefully Predict Coronary Artery Disease?

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Abstract

Aims: We have investigated to what extent Metabolic Syndrome (MS) is related to Coronary Artery Disease (CAD) incidence and we tried to determine a metric parameter combining MS quantitative components to be used as a screening tool to diagnose CAD.

Materials and methods: 239 patients and 244 control subjects were investigated for clinical, biochemical, anthropometric and angiographic information. CAD is defined as 50% stenosis on the left main coronary artery or multiple significant (≥ 70% stenosis) in more than one coronary artery. The diagnosis of MS was based on the IDF and AHA/NHLBI definition. The computer model HOMA 2 was used to determine HOMA-β, HOMA-S and HOMA-IR. Triglycerides (TG), High Density Lipoprotein cholesterol (cHDL), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), HOMA-IR and Waist Circumference (WC) were used to calculate the different MS markers. The area under curve of ROC curves were used to compare the powers of these MS markers.

Results: MS was significantly related to the CAD. Each MS quantitative component was a significant discriminating factor for CAD. FPG followed by SBP were the principal predictive factors of CAD. A metric parameter combing MS qualitative components [(TG/cHDL) × (HOMA-IR × WC)] + SBP was more accurate to estimate CAD risk. Its cut-off point was 247.1

Conclusion: MS was associated with CAD. This marker, with sensitivity and specificity of 86.2 and 73.0 per cent can be used either to diagnose or to predict CAD incidence.

Keywords: Metabolic syndrome; Coronary artery disease; Coronary angiography; Metric parameter; CAD prediction

Introduction

For the past decades; Tunisian population showed economic evolution which explained social change: life style, diet choices and sedentary. Metabolic Syndrome (MS) is an increasing occurrence. It has serious health consequences. The MS is a complex nosological entity characterized by the clustering of several cardiovascular risk factors, such as abdominal obesity, elevated triglycerides (TG), low High Density Lipoprotein cholesterol (cHDL), elevated Blood Pressure (BP) and high Fasting Plasma Glucose (FPG). MS is the concurrence of multiple metabolic abnormalities associated with the development and progression of atherosclerosis [1]. Meta-analyses showed that MS increases the risk of cardiovascular disease and mortality [2-4]. However, the major limitation of MS was the use of dichotomous cut- off points. Moreover, there was a constellation of combinations of three to five criteria. Coronary Artery Disease (CAD) is a narrowing or blockage of the arteries and vessels that provide oxygen and nutrients to the heart which are caused by atherosclerosis. It is a chronic, complex and progressive pathological process in large- and medium-sized arteries. There are multiple potential mechanisms contributing to susceptibility to atherosclerosis. Injury of the endothelium, migration of monocytes/macrophages, and the regulatory network of growth factors and cytokines are important in the development of atherosclerosis. Hypertension, dyslipidemia, increased free radicals and diabetes causes chronic inflammation of the vascular wall and abnormal immune response. Their formation is triggered by endothelial cell activation and dysfunction causing the release of vocative molecules and cytokines, which stimulate an inflammatory response and recruitment/migration of leukocytes into the arterial wall [5]. We assess the impact of MS on the presence of Coronary Artery Disease (CAD).We establish the best cut-off points of each MS component associated with the incidence of CAD. We seek to determine a sole metric parameter combining MS quantitative components to be used as a screening tool to diagnose CAD.

Materials and Methods

Study population

We collected clinical, biochemical, anthropometric and angiographic information from 239 patients (128 men and 111 women) who underwent elective coronary angiography at the Cardiology Department of the University Hospital of Monastir, Tunisia. 244 healthy subjects of both sexes (125 men and 119 women) were undergoing a routine check up which included medical history, physical examination, an ECG, a chest X-ray, and biological analysis were used as a control group. All the participants gave their written informed consent prior to their participation. The study was approved by the ethical committee of the Hospital. Coronary angiography was performed by the Judkins technique. The grades of luminal narrowing were determined according to the consensus opinion of two experienced interventional cardiologists. CAD is defined as 50% stenosis on the left main coronary artery or multiple significant (≥ 70% stenosis) in more than one coronary artery [6].

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Diagnostic criteria for metabolic syndrome

The diagnosis of MS was based on the IDF and AHA/NHLBI definition, which requires the presence of at least three of the following criteria: the central (abdominal) obesity (defined as waist circumference (WC) ≥ 94 cm in men and ≥ 80 cm in women), the raised TG ≥ 1.70 mmol/L (drug treatment for elevated triglycerides is an alternate indicator), the reduced cHDL <1.04 mmol/L in men and <1.29 mmol/L in women (or specific treatment for this lipid abnormality), the elevated Systolic Blood Pressure (SBP) ≥ 130 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 85 mmHg (antihypertensive drug treatment in a patient with a history of hypertension was an alternate indicator), and the elevated FPG ≥ 5.56 mmol/L or previously diagnosed type 2 diabetes [7].

Anthropometric measurements

Height and weight were measured according to a standardized protocol in the study population, with subjects wearing light clothing and no shoes. Body Mass Index (BMI) was calculated by dividing weight in kilograms by height in square meters (kg/m^2). The waist circumference was measured in the horizontal plane at the midpoint between the lowest rib and the iliac crest. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured to the nearest 5 mmHg with a mercury sphygmomanometer, with subjects in a supine position and having relaxed for 5 minutes.

Biochemical analysis

The blood samples of the study population were collected in the morning after a 12-hour fasting period, heparinized plasma was immediately obtained by blood centrifugation at 4°C at 3000 rpm for 15 min. All analyses were carried out on Cobas 6000™ analyzer (Roche Diagnostics Mannheim, Germany), in biochemistry and toxicology laboratory of the Hospital. Serum Triglycerides (TG), serum High Density Lipoprotein cholesterol (cHDL) and Fasting Plasma Glucose (FPG) were measured by enzymatic methods. Fasting plasma insulin (FPI) was measured by Electrochemiluninescence Immuno Assay (ECLIA). The computer model HOMA 2 was used to determine β-cell function (HOMA-β%), insulin sensitivity (HOMA-S%), and insulin resistance (HOMA-IR) from paired fasting glucose (mmol/L) and insulin (mIU/L) concentrations [8].

Statistical analysis

Data were analyzed by SPSS 17.0 for Windows. Continuous results that satisfied a normal distribution are expressed as mean ± Standard Deviation (SD). Those results that provided abnormal distribution data are expressed as median and quartile; and frequencies for qualitative variables. Comparisons among groups were assessed using the independent-sample *t* test for quantitative variables and Pearson's chi-square test for qualitative variables. The probability of CAD occurrence in relation to MS components, were estimated as odds ratio (OR) [95% confidence interval (CI)]. The area under curve (AUC) of the receiver operating characteristic (ROC) curves was used for predicting a better marker for CAD. ROC curve analysis was employed to select the best cut-off points of each marker which have the highest predictive value for CAD. The pair index (1-specificity, sensitivity) was used to determine optimal cut-off points. A two-sided $p<0.05$ was considered as statically significant.

Results

Among the 239 patients who were enrolled, 128 were men (53.6%) aged from 33 to 83 years (58.5 ± 9.4) and 111 were women (46.4%) aged 30 to 76 years (57.0 ± 9.8). Healthy subjects included 125 men (51.2%) aged 40 to 69 years (55.6 ± 7.5) and 119 women (48.8%) aged 37 to 72 years (57.3 ± 7.1). Table 1 shows that patients have higher SBP, DBP, BMI, TG, TC, cLDL, FPG and FPI; and reduced cHDL than control subjects. We also noted an increase in HOMA IR and a decrease in HOMA β and HOMA S in patients.

The prevalence rates of MS were higher among patients compared to control subjects respectively 183 (76.6%) and 26 (10.7%). Table 2 shows that MS^+ patients have higher BMI, WC, SBP, DBP, TG, FPG and Number of MS Components (NC); and lower cHDL compared to patients MS^-. The same result was found in control subjects with and without MS. Also values of these parameters were higher among MS^+ patients compared to MS^+ control subjects. CAD was found significantly higher in MS^+ patients compared to MS^- patients [183 (76.6%) vs. 56 (23.4%), $p<0.001$].

The Odds ratios (OR) for CAD risk of different MS components are represented in table 3. FPG following by SBP were the principal predictive factors of CAD in MS^+ and MS^- groups. We noted that MS increases significantly those OR [(FPG 1.82 vs. 5.49), (SBP 1.25 vs. 1.83)]. Table 4 shows that each MS quantitative component was a significant discriminating factor for CAD. Furthermore, the cut-off point for prediction CAD of each MS component was in concordance of IDF criteria definition. The largest AUC were obtained through cHDL followed by HOMA-IR and SBP.

Furthermore, the largest AUC were obtained with HOMA-IR, followed by FPG, indicating that the model with HOMA-IR was superior in estimating impaired glycaemia in CAD. The ROC curves plotted shows that TG/cHDL ratio expresses better dyslipidemia in CAD than TG and cHDL separately [AUC was 0.821, 0.766 and 0.790; respectively]. Moreover, SBP was more informative about hypertension in CAD either (SBP+DBP) sum or (SBP x DBP) product [AUC was 0.830, 0.783 and 0.778; respectively]. We noted a significant stepwise increase in AUC of MS marker with each additional quantitative MS component (Table 3). The largest AUC was obtained with [(TG/cHDL) × (HOMA-IR × WC)] + SBP ratio, indicating that it was more

Variable	Controls (n=244)	Patients (n=239)	*p*
Age (years)	57 (52-62)	59 (52-64)	0.058
Gender M/F [n (%)]	125/119 (51.2/48.8)	128/111 (53.5/46.5)	0.609
Diabetes [n (%)]	22 (9.4)	113 (47.2%)	<0.001
Hypertension [n (%)]	29 (11.9)	92 (38.5)	<0.001
SBP(mmHg)	120 (120-125)	140 (130-150)	<0.001
DBP(mmHg)	80 (75-80)	85 (80-90)	<0.001
BMI (kg/m^2)	24.7 (23.9-25.9)	27.6 (25.4-29.4)	<0.001
TG (mmol/L)	1.12 ± 0.47	1.75 ± 0.75	<0.001
TC (mmol/L)	4.56 (4.21-4.99)	5.00 (4.07-5.75)	<0.001
cLDL (mmol/L)	3.00 (2.62-3.31)	3.30 (2.54-3.99)	<0.001
cHDL (mmol/L)	1.18 (1.09-1.46)	0.96 (0.80-1.20)	<0.001
FPG (mmol/L)	4.88 ± 0.82	6.84 ± 1.86	<0.001
FPI (mIU/L)	7.48 (6.61-8.99)	12.65 (9.48-13.28)	<0.001
HOMA-β%	103 (88-123)	78 (52-96)	<0.001
HOMA-S%	103 (86-117)	57 (53-80)	<0.001
HOMA-IR	1.0 (0.9-1.2)	1.8 (1.3-1.9)	<0.001

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; TG: Triglycerides; TC: Total Cholesterol; cLDL: Low lipoprotein Density Cholesterol; cHDL: High Lipoprotein Density Cholesterol; FPG: Fasting Plasma Glucose; FPI: Fasting Plasma Insulin; HOMA-β%: %β cell function; HOMA-S%: %cell Insulin Sensitivity; HOMA-IR: Insulin Resistance

Table 1: Biochemical and anthropometric parameters tested on patients and control subjects.

	Control subjects n=244			Patients n=239		
Variables	**MS⁻ n = 218**	**MS+ n = 26**	***p***	**MS⁻ n = 56**	**MS+ n = 183**	***p***
Age (years)	57 (51-62)	57 (55-63)	0.272	59 (51-67)	59 (52-64)	0.410
Gender M/ F (%)	109/109 (50.0/50.0)	16/10 (61.5/38.5)	0.266	30/26 (53.5/46.5)	90/93 (49.2/50.8)	0.183
Diabetes [n (%)]	2 (0.9)	2 (7.7)	0.010	11 (19.6)	50 (27.3)	<0.001
Hypertension [n (%)]	4 (1.8)	9 (34.6)	<0.001	29 (51.8)	150 (82.0)	<0.001
SBP (mmHg)	120 (115-120)	125 (120-135)	<0.001	125 (120-140)	140 (130-150)	<0.001
DBP (mmHg)	80 (70-80)	80 (80-90)	<0.001	80 (70-85)	85 (80-90)	<0.001
BMI (kg/m^2)	24.5 (23.7-25.7)	26.4 (26.0-26.8)	<0.001	24.4 (23.5-28.1)	27.9 26.5-29.4)	<0.001
Men WC (cm)	93 (87-95)	96(95-96)	<0.001	93 (92-96)	99 (95-101)	<0.001
Women WC (cm)	79 (77-86)	92(89-92)	<0.001	79 (79-97)	93 (89-98)	<0.001
TG (mmol/L)	1.03 ± 0.40	1.87 ± 0.31	<0.001	1.26 ± 0.49	1.90 ± 0.75	<0.001
Men cHDL(mmol/L)	1.14 (1.04-1.17)	0.92 (0.88-1.05)	<0.001	1.00 (0.88-1.09)	0.81 (0.68-1.01)	<0.001
Women cHDL(mmol/L)	1.46 (1.37-1.56)	1.05 (0.91-.1.19)	<0.001	1.26 (1.12-1.35)	1.10 (0.92-.1.28)	<0.001
TG/cHDL	0.84 (0.72-1.42)	2.11 (1.70-2.33)	<0.001	1.06 (0.81-1.38)	1.97 (1.33-2.52)	<0.001
FPG (mmol/L)	4.76 ± 0.59	5.85 ± 1.12	<0.001	5.63 ± 1.59	7.21 ± 1.79	<0.001
FPI (mIU/L)	7.24 (6.58-8.44)	12.70 (10.71-13.76)	<0.001	8.91 (7.40-11.89)	12.83 (11.58-13.52)	<0.001
HOMA-β%	103(87-123)	115(78-126)	<0.001	94 (84-112)	69 (52-93)	<0.001
HOMA-S%	105(92-119)	59(55-73)	<0.001	84 (64-105)	55 (52-61)	<0.001
HOMA-IR	0.9(0.8-1.1)	1.7(1.4-1.8)	<0.001	1.2(1.0-1.6)	1.8 (1.6-1.9)	<0.001
NC	0 (0-1)	3 (3-4)	<0.001	2 (1-2)	3 (3-4)	<0.001

MS⁻: without Metabolic Syndrome; MS⁺: with Metabolic Syndrome; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; WC: Waist Circumference; TG: Triglycerides; cHDL: High Density Lipoprotein cholesterol; FPG: Fasting Plasma Glucose; FPI: Fasting Plasma Insulin; HOMA-β%; %β cell function; HOMA-S%: %cell insulin Sensitivity; HOMA-IR: Insulin Resistance; NC: Number of MS Components.

Table 2: Biochemical and anthropometric parameters tested in study population.

	Components	Odds ratio (95%CI)	*p*
MS⁻ group	SBP (mmHg)	1.25 (1.15-1.36)	<0.001
	DBP (mmHg)	0.77 (0.69-0.87)	<0.001
	WC (cm)	1.03 (0.97-1.09)	0.302
	TG (mmol/L)	1.28 (0.51-3.24)	0.594
	cHDL (mmol/L)	0.01 (0.01-0.08)	<0.001
	FPG (mmol/L)	1.82 (1.21-2.73)	0.004
MS⁺ group	SBP(mmHg)	1.83 (1.37-2.45)	<0.001
	DBP(mmHg)	0.44 (0.30-0.67)	<0.001
	WC (cm)	1.24 (1.05-1.46)	0.011
	TG(mmol/L)	0.68 (0.23-2.31)	0.544
	cHDL (mmol/L)	0.01 (0.00-0.41)	0.013
	FPG (mmol/L)	5.49 (2.38-12.69)	<0.001

CI: Confidence Interval; MS⁻: without Metabolic Syndrome; MS⁺: with Metabolic Syndrome; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WC: Waist Circumference; TG: Triglycerides; cHDL: High Density Lipoprotein cholesterol; FPG: Fasting Plasma Glucose

Table 3: Odds ratios for CAD risk of different MS quantitative components.

Variables	AUC (95% C I)	*p*	Cut-off point	% sensitivity	% Specificity
Sole MS components					
SBP (mm Hg)	0.830 (0.791-0.870)	<0.001	125	81.2	74.6
DBP (mm Hg)	0.675 (0.626-0.724)	<0.001	80	81.2	27.0
WC (cm)	0.757 (0.714-0.799)	<0.001	92.5	71.5	62.7
TG (mmol/L)	0.766 (0.724-0.807)	<0.001	1.28	73.2	69.3
cHDL(mmol/L)	0.790 (0.751-0.830)	<0.001	1.08	75.4	68.2
FPG (mmol/L)	0.836 (0.798-0.873)	<0.001	5.23	79.9	79.5
HOMA-IR	0.844 (0.808-0.880)	<0.001	1.2	83.3	73.4
Mixed MS components					
TG/cHDL	0.821 (0.785-0.857)	<0.001	0.81	88.7	53.3
(TG/cHDL)x HOMA-IR	0.874 (0.843-0.905)	<0.001	1.25	84.9	72.1
(TG/cHDL) x (HOMA-IR x WC)	0.877 (0.846-0.908)	<0.001	123.3	84.9	72.5
[(TG/cHDL) x (HOMA-IR x WC)] + SBP	0.890 (0.861-0.919)	<0.001	247.1	86.2	73.0

AUC: Area Under Curve; CI: Confidence Interval; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WC: Waist Circumference; TG: Triglycerides; cHDL: High Density Lipoprotein cholesterol; FPG: Fasting Plasma Glucose; HOMA-IR: Insulin Resistance.

Table 4: Receiver Operating Characteristics curves analysis and cut-off values for sole and mixed MS quantitative components to CAD prediction.

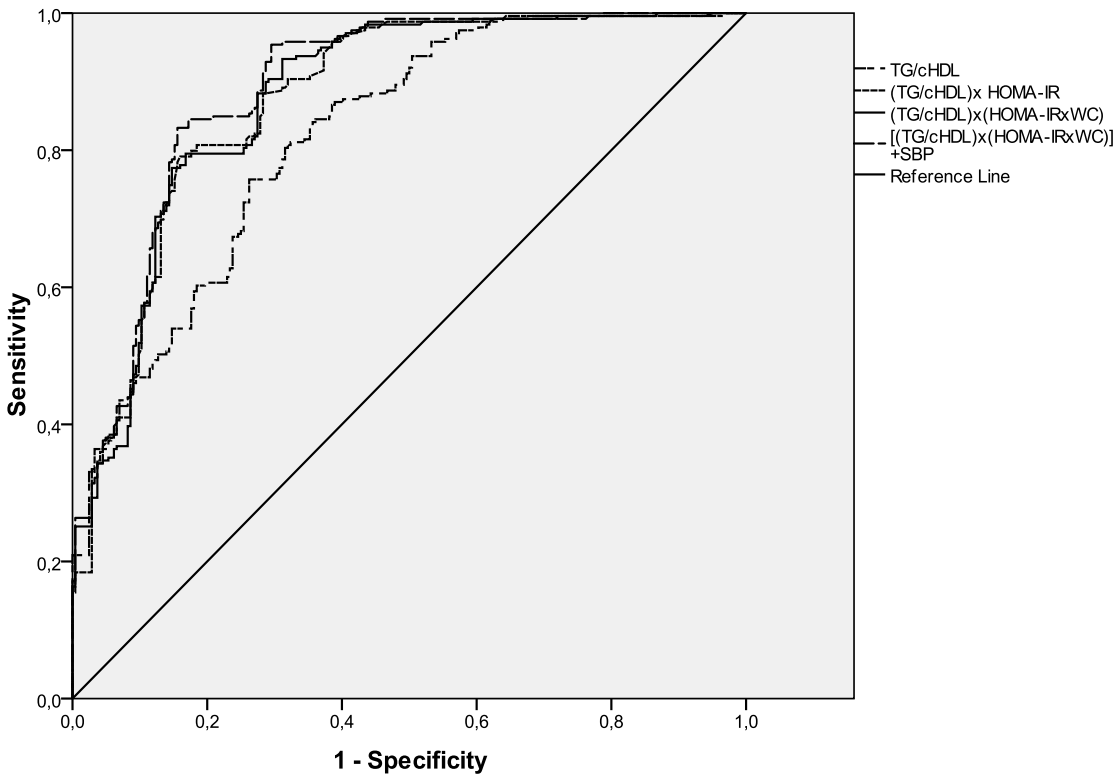

Figure 1: ROC curves of TG/cHDL, (TG/cHDL) × HOMA-IR, (TG/cHDL) × (HOMA-IR × WC) and [(TG/cHDL) × (HOMA-IR x WC)] + SBP for CAD prediction.

accurate to estimate CAD risk (Figure 1). The optimal cut-off point for prediction of CAD in present study was with sensitivity and specificity of 86.2 and 73.0 per cent.

Discussion

Metabolic Syndrome (MS), a pro-inflammatory state with hypertension, diabetes, dyslipidemia and obesity is presumed to be a close associate of Coronary Artery (CAD). However, the exact mechanism by which MS facilitates perpetuation of CAD is yet to be fully understood. Moreover, the impact of the components of MS as well as MS as a group, on CAD is not clearly elucidated until now. We evaluate that MS as a simple diagnostic tool to identify subjects at high risk of CAD. The major limitation of MS was the use of binary cut-off point components. Moreover, there was a mosaic of combinations of three to five criteria which make it very unlikely that all subgroups are similar entities from a pathphysiology standpoint and a clinical prognosis [9]. Some studies have found that the presences of MS need not to be more informative than the sum of its risk factors [10,11].

In accordance with our results, the number of MS criteria may be more useful than MS to predict the severity of CAD [12]. The increased risk appears to be related to clustering the risk factor associated with MS [13,14]. Our data shows that FPG followed by SBP were the principal predictive factors of CAD. However, abnormal glucose metabolism precedes Type 2 Diabetes mellitus (T2D), which was a well-know risk factor for cardiovascular disease, and develops over a protracted period during a progressive resistance to the action of insulin [15,16]. Insulin Resistance (IR) results in hyperinsulinemia, hyperglycaemia due to enhanced hepatic gluconeogenesis and glucose output, and an increase in plasma Fatty Acids (FAs) due to reduced suppression of lipolysis in adipose tissue. The increased FAs flux to the liver results in increased production of apolipoprotein B containing TG-rich Very Low Density Lipoprotein (VLDL) which results in hyper triglyceridemia and reduced plasma levels of cHDL [17,18].

In our study, we noted that each MS quantitative component was a significant discriminating factor for CAD. Moreover, HOMA-IR was superior in estimating impaired glycaemia in CAD than FPG. There is clinical evidence for a link between IR with essential hypertension [19]. All relevant definitions of MS hold that abdominal visceral obesity is central to development of diabetes and cardiovascular accidents [20]. TG/cHDL ratio, the major quantitative change associated with the insulin resistance [21,22]. Furthermore, many studies demonstrated the relationship between IR and obesity, and dyslipidemia [23,24]. In our approach to establish a metric MS marker; we multiplied (TG/cHDL) ratio by (HOMA-IR x WC). Moreover, several studies have reported evidence that patients with essential hypertension are insulin resistant and hyperinsulinemic compared with normotensive individuals [25,26]. Thus, we added SBP component to the previous ratio. We found a significant stepwise increase in CAD prediction with each additional quantitative MS components. The [(TG/cHDL) × (HOMA-IR × WC)] + SBP was more accurate parameter to estimating CAD risk.

We can explain this impact by synergistically interact between individual components in accelerating the progression of arthrosclerosis. We seek to determine a sole metric MS parameter combining MS quantitative components to use in the prevention of CAD. In fact, this metric tool, with sensibility=86.2% and specificity=73.0 can be used either to diagnose or to predict CAD incidence. To confirm our funding Meta analysis ought to be conducted.

Conclusion

Individual MS components may interact synergistically in accelerating the progression of CAD. In Tunisia, cardiologists are positioned to play an important role to identify patients at high risk of CAD, using this metric MS parameter either to diagnose or to predict CAD incidence.

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