Relationship between the severity of coronary artery disease and metabolic syndrome score

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The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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June 2008

This certifies that the Master's Thesis of

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June 2008

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ABSTRACT

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The metabolic syndrome (MS) has been reported as a potential risk factor of early coronary artery disease (CAD). The objective of our study was to compare the heterogenous phenotype of MS positive group with those of MS negative group, to assess any relationship between the MS score and the angiographic severity of CAD, and to assess the predictive ability of the MS and its components. MS was defined by the National Cholesterol Education Program Adult Treatment Panel III criteria. CAD angiographic severity was evaluated with a Gensini scoring system. Body mass index, hypertension, dysglycemia parameters, lipid profiles and some biochemical markers were significantly different between MS positive and MS negative group. MS score correlated with the angiographic severity of CAD. High fasting blood glucose was a most powerful predictor, and some clusters with hypertension and low high density lipoprotein cholesterol may play a synergic role as the risk factors.

Key words : Metabolic syndrome; coronary artery disease

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I. INTRODUCTION

The metabolic syndrome (MS) is the concurrence in an individual of multiple metabolic abnormalities associated with the development and progression of atherosclerosis. Since 1988, Reaven first definition of the MS included these components: hyperglycemia, abdominal obesity, hypertriglyceridemia, low high density lipoprotein (HDL) cholesterol concentration, and hypertension.[1] There are several definitions for the MS. The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) definition are the most widely used and focused explicitly on the risk of cardiovascular disease.[2, 3] In the report the MS has been defined as the presence of at least three among five quantitatively defined markers; abdominal obesity, high triglycerides (TG), low level of HDL cholesterol, high blood pressure (BP) and high fasting blood glucose (FBG).[2, 3]

The MS is becoming increasingly common, and it represents a global public health problem.[4, 5] In Framingham Heart Study, the prevalence of the MS was 26.8 % in men and 16.7 % in women in the early 1990s. After eight years of

follow up, there was an age adjusted 56 % increase in prevalence among men and a 47 % increase among women.[6] Three meta-analyses, which included many of the same studies, found that the MS increases the risk for incident cardiovascular disease and all cause of mortality.[7-9] The increased risk appears to be related to the risk factor clustering associated with the MS.[6, 10] The individual components may interact synergistically causing of accelerating the progression of atherosclerosis.[11]

There is a significant overlap between diabetes mellitus (DM) and the MS.[12] A study has shown that the presence of MS increased the risk of cardiovascular events several fold even in patients with DM.[13] Type 2 DM has long been recognized as a significant risk factor for CAD and has been acknowledged as a CAD equivalent.[3] However, the additive predictive value of metabolic syndrome for cardiovascular disease is still debated.[14]

The objective of our study was to compare the clinical, biochemical and angiographic characteristics of MS positive group with MS negative group in patients who underwent elective coronary angiography, and to assess any relationship between the MS score and the severity of CAD at coronary angiography. Additionally, we intended to assess and distinguish the predictive ability of the MS, its individual components and different clusters of the MS.

II. MATERIALS AND METHODS

1. Subjects

From January 1, 2007 to December 31, 2007, we collected clinical, biochemical and angiographic information in 632 consecutive patients who underwent elective coronary angiography (394 men, 61.0 ± 10.6 years of age) at the Heart Center, Yongdong Severance Hospital, Yonsei University College of Medicine. All patients were Asian origin. Patients with recent MI, which could potentially affect blood glucose and lipid levels, were excluded from this study.

All patients had a physical examination with anthropometric measurements including height, weight and body mass index (BMI). They answered a questionnaire about cardiovascular risk factors such as hypertension, DM, dyslipidemia, smoking and so on.

2. Definition

A. Metabolic syndrome

The NCEP ATP III definition of the MS requires the presence of at least three of the following five abnormalities: 1) hyperglycemia: FBG > 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose, 2) high arterial BP: BP > 130/85 mmHg or drug treatment for hypertension, 3) hypertriglyceridemia: TG > 150 mg/dL (1.7 mmol/L), 4) low HDL cholesterol: HDL cholesterol < 40 mg/dL (1.0 mmlo/L) in men or < 50 mg/dL (1.3 mmol/L) in women, 5) central adiposity: Waist > 90 cm in men or > 80 cm in women.[2, 3, 15] Since data on waist circumference were not available, waist criterion modified into BMI of more than 25 kg/m^2.[16] A previous diagnosis of type 2 DM was regarded to be an evidence of an high FBG.

B. Framingham risk score

The Framingham risk score (FRS) add points for age, presence of DM, smoking habitus, low density lipoprotein (LDL) cholesterol, HDL cholesterol, and BP to derive an estimated risk of developing coronary heart disease within 10 years.17

3. Biochemical tests

Venous sampling was collected in early morning after an overnight fast prior to elective angiography using standard venipuncture technique. Insulin resistance was evaluated by the homeostatic model assessment (HOMA) as described by Matthews et al[18]; which was calculated as the product of fasting insulin level (divided by 6 to express results in microunits per milliliter) and fasting glucose level (millimoles per liter) divided by 22.5. Normoglycemia, impaired fasting glucose, and DM were categorized as per the recent definitions of the American Diabetes Association.[19]

4. Angiographic assessment

All subjects underwent catheterization and coronary angiography, using standard techniques. The Gensini score was used in the present study to assess the burden of coronary atherosclerosis. The system yields a qualitative and quantitative evaluation of the coronary angiogram; it grades the narrowing of the lumen of the coronary artery as 1 for ≤25% narrowing, 2 for 26–50% narrowing, 4 for 51–75% narrowing, 8 for 76–90% narrowing, 16 for 91–99% narrowing, and 32 for total occlusion. Next, this primary score is multiplied by a factor that takes into account the importance of the position of the lesion in the coronary arterial tree (5 for the left main coronary artery, 2.5 for the proximal left anterior descending artery or proximal left circumflex artery and

1.5 for the mid-region, 1 for the distal left anterior descending artery, and 1 for the mid-distal region of the left circumflex artery or right coronary artery). In this study, the Gensini score was expressed as the sum of the scores for all three coronary arteries in order to evaluate the entire extent of CAD. The grades of luminal narrowing were determined based on the consensus opinion of two experienced interventional cardiologists.[20]

5. Statistical analyses

The patients were divided into 2 groups according to the prevalence of MS or 6 groups according to the number of constituents (0 to 5) of the MS score. We used the quantitative and sex-specific definitions of NCEP ATP III to identify these markers. All data were analyzed using statistical software SAS version 9.1. Baseline demographic and laboratory data are presented as mean (standard deviation) for continuous variables and frequencies for discrete variables. Comparisons among groups used analysis of variance for continuous variables and t-testing for discrete variables. Correlations between MS score or FRS and Gensini score were examined by linear regression analysis. The probability in the occurrence of CAD in relation to the MS, its single traits and their combinations were estimated as odds ratio (OR) (95% CI).

III. RESULTS

1. Incidence of MS and frequency of its constituents with and without MS

Of the 632 patients undergoing coronary angiography for the evaluation of CAD, 283 (44.8%) was diagnosed as MS.

Table 1. Cumulative frequency of metabolic components according to metabolic score

	0	1	2	3	4	5
High BMI	0 (0%)	25 (22.9%)	82 (40.6%)	107 (69%)	80 (80.8%)	29 (100%)
High FBG	0 (0%)	15 (13.8%)	62 (30.7%)	83 (53.5%)	77 (77.8)	29 (100%)
High BP	0 (0%)	38 (34.9%)	138 (68.3%)	125 (80.6%)	89 (89.9%)	29 (100%)
High TG	0 (0%)	4 (3.7%)	28 (16.3%)	49 (33.2%)	62 (62.6%)	29 (100%)
Low HDL	0 (0%)	27 (24.8%)	94 (46.5%)	101 (65.2%)	88 (88.9%)	29 (100%)

(%): cumulative percentage of metabolic components

The distribution of patients with 0 to 5 MS score is listed in table 1. In most groups, high BP was the most frequent abnormality, followed by low HDL, high BMI, high FBG and high TG.

2. Clinical and biochemical characteristics of prevalence of MS

Table 2 shows the clinical characteristics, prevalence of risk factors, lipid profiles, glucose homeostasis characteristics and other biochemical markers including inflammatory markers by presence (n=283) or absence (n=349) of MS.

Table 2. Clinical and biochemical characteristics of prevalence of MS

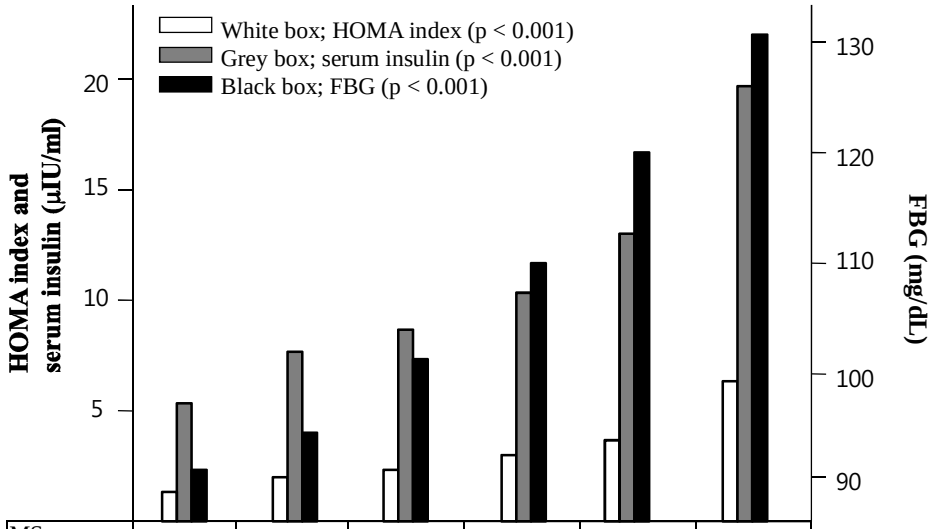
	MS – (N=349)	MS + (N=283)	P value
Age (years)	61.02 ± 10.78	61.00 ± 10.36	0.984
Male gender (%)	63.90 %	60.42%	0.371
Height (cm)	162.87 ± 8.37	162.70 ± 8.9	0.799
Weight (kg)	64 ± 9.91	70.30 ± 10.20	<0.001
BMI (kg/m2)	24.17 ± 2.76	26.48 ± 2.62	<0.001
Smoking (%)	151 (43.26 %)	131 (46.62%)	0.401
History of hypertension (%)	176 (50.43%)	243 (85.87%)	<0.001
History of DM (%)	45 (12.89%)	139 (49.12%)	<0.001
Lipid profiles			
Total cholesterol (mg/dL)	152.86 ± 32.45	160 ± 35.86	0.006
TG (mg/dL)	101.43 ± 42.50	166.76 ± 49.92	<0.001
HDL (mg/dL)	47.08 ± 14.49	38.97 ± 8.07	<0.001
LDL (mg/dL)	92.77 ± 28.16	97.61 ± 32.80	0.046
T chol/HDL ratio	3.401 ± 0.90	4.24 ± 1.13	<0.001
Lipoprotein(a) (mg/dL)	24.34 ± 28.37	20.97 ± 29.30	0.146
Glucose homeostasis			
FBG (mg/dL)	98.72 ± 19.72	115.84 ± 36.99	<0.001
Serum insulin (μIU/mL)	7.79 ± 7.78	12.45 ± 15.20	<0.001
HOMA index	1.97 ± 2.40	3.6 ±4.67	<0.001
Biochemical markers			
Fibrinogen (mg/dL)	325.97 ± 75.78	334.46 ± 88.48	0.199
WBC (10^3/μL)	7161.15±2260.99	7470.52±2151.42	0.080
Hs-CRP (mg/L)	4.89 ± 13.79	5.79 ± 17.32	0.464
ESR (mm/hr)	13.73 ± 14.17	16.49 ± 17.75	0.036
Homocysteine (μmol/L)	8.33 ± 3.52	9.54 ± 7.49	0.008
BNP (pg/mL)	98.51 ± 324.30	107.29 ± 408.58	0.766
Cystatin C (mg/L)	0.90 ± 0.53	1.01 ± 0.61	0.026

Characteristics of age (average 61.01±10.57 years), gender (62.16% male), smoking (44.92%) and height (average 162.76±8.63) did not differ between two groups.

The individual components of MS were highly prevalent in these MS positive patients as compared to those who were negative. The average BMI, level of TG and history of hypertension and DM were significantly higher in MS positive group. The level of HDL was significantly lower in MS positive group.

Patients with MS also have significantly increased values of total cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol ratio, FBG, serum insulin and HOMA insulin resistance index. Among biochemical markers, ESR, homocysteine and cystatin C were significantly higher in MS positive group.

3. Glucose homeostasis characteristics in relation to MS score



MS score	0	1	2	3	4	5
HOMA index	1.42 ± 1.09	1.73 ± 1.65	2.18 ± 2.83	3.08 ± 3.83	3.74 ± 4.49	6.51 ± 7.52
Serum insulin	6.13 ± 4.62	7.15 ± 4.86	8.39 ± 9.22	10.79 ± 10.87	12.96 ± 18.77	19.20 ± 18.68
FBG	91.81 ± 8.11	94.73 ± 15.18	102.16 ± 22.53	109.89 ± 32.09	120.65 ± 42.43	131.28 ± 35.85

Figure 1. Glucose homeostasis characteristics in relation to MS score.

Figure 1 indicates that as the MS score increased, so did FBG, serum insulin and the HOMA index. The degree of change of the indexes of dysglycemia is

worth noting. Glucose increased by 43% from an MS score of 0 to 5, whereas serum insulin and HOMA index increased by 213% and 358%, respectively.

4. Prevalence of CAD and association between MS score and severity of CAD

CAD was present at angiography in 86.9% (n=549), and 13.1% (n=83) had normal to minimal lesion of coronary artery anatomy.

Table 3. Angiographic characteristics of prevalence of MS

	MS – (N=349)	MS + (N=283)	p value
Gensini score	15.47 ± 23.39	23.31 ± 29.21	0.002
Normal to minimal	47 (13.46%)	36 (12.72%)	0.681
1VD	98 (28.08%)	72 (25.44%)	
Multivessel dz	204 (58.45%)	175 (61.84%)	

Table 3 demonstrates that compared to patients without the MS, there were tendencies for higher rate of multivessel disease and lower rate of normal coronary artery in MS positive patients, however the differences with MS negative group did not reach statistically significance. However MS positive patients had a significantly higher Gensini score (p=0.002).

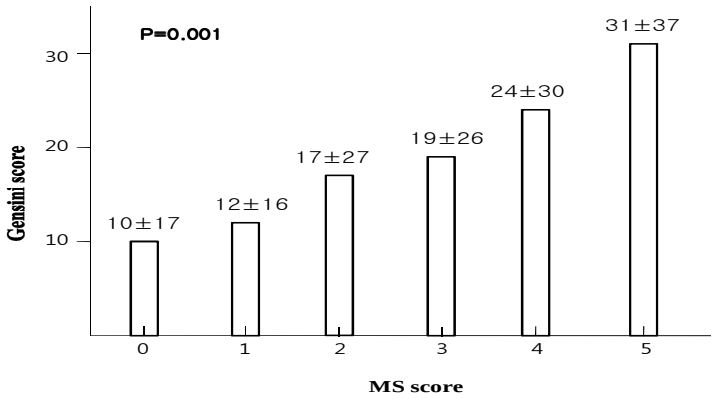


Figure 2. Relationship between MS score and Gensini score.

There was a clear relation between the MS score and CAD severity. Figure 2 demonstrates that Gensini score becomes more elevated with increasing MS score. There was also a positive correlation between the FRS and Gensini score. By linear regression analyses, MS score was effective at predicting CAD as well as FRS. (both R^2 value 0.03)

5. Predictive ability for CAD of MS and its components

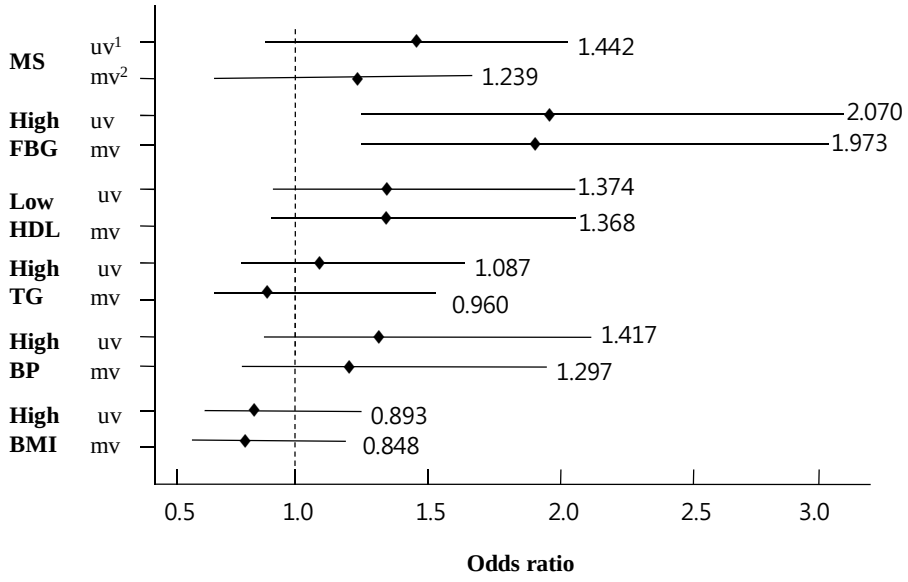


Figure 3. Odds ratio plots for the MS and its component parts as predictors of angiographic CAD. ([1] univariate analysis, [2] multivariate analysis)

The predictive abilities for angiographic CAD of the MS and its components are shown in figure 3. MS alone did not predict presence of CAD. Individually, high FBG was the only predictive factor for CAD in univariate analysis (OR 2.070, 95% CI 1.371-3.124, p=0.001), and multivariate analysis

did not diminish this association (OR 1.973, 95% CI 1.297-3.000, p=0.002). Low HDL, high BMI, high BP and high TG were not predictive of CAD in univariate and multivariate analyses.

6. Impact of the different combinations of MS components for CAD in high FBG

Table 4. Odds ratios (95% CI) for CAD of different phenotypes in high FBG

Phenotype	Odds ratio (95% CI)	P value
HFBG[1] alone	2.070 (1.371-3.124)	<0.001
HFBG+HBP[2]	2.579 (1.492-4.457)	<0.001
HFBG+LHDL[3]	2.489 (1.441-4.299)	0.001
HFBG+HTG[4]	1.864 (0.992-3.505)	0.053
HFBG+HBMI[5]	1.716 (0.990-2.973)	0.054
HFBG+HBP+LHDL	3.731 (1.748-7.797)	<0.001
HFBG+HBP+HTG	2.677 (1.229-5.832)	0.013
HFBG+HBP+HBMI	2.963 (1.440-6.098)	0.003
HFBG+LHDL+HTG	2.286 (1.066-4.902)	0.034
HFBG+LHDL+HBMI	1.699 (0.837-3.449)	0.143
HFBG+HTG+HBMI	1.532 (0.702-3.346)	0.284
HFBG+HBP+LHDL+HTG	3.256 (1.190-8.908)	0.022
HFBG+HBP+LHDL+HBMI	3.167 (1.223-8.202)	0.018
HFBG+HBP+HTG+HBMI	2.412 (0.920-6.324)	0.073
HFBG+LHDL+HTG+HBMI	1.358 (0.555-3.323)	0.503
HFBG+HBP+LHDL+HTG+HBMI	1.769 (0.572-5.471)	0.322

[1] high FBG, [2]high BP, [3]low HDL, [4]high TG, [5] high BMI

The ORs for CAD risk in patients with high FBG are presented in table 4. Patients without another trait had an OR of 2.070. High BP as companion increased the OR significantly to 2.579. The only other single trait of significance was low HDL (OR 2.489). For triads meeting the MS diagnosis it were the clusters with high BP representing with the highest risk: OR 3.731 in combination with low HDL. The OR for the combination with high BP plus high TG, high BP plus high BMI and low HDL plus high TG was in the same range, whereas the triads with low HDL plus high BMI and high TG plus high

BMI did not increase the risk for CAD. Among the quartets only the combinations including high BP plus low HDL were associated with an increased risk (OR 3.256 and 3.167). The OR for the quintet was not significantly increased (OR 1.769, 95% CI 0.572-5.471, p=0.322). High FBG, high BP and low HDL are the significant contributors to CAD risk. There is no stepwise increase from triads to quintet.

IV. DISCUSSION

The MS is a constellation of risk factors of metabolic origin that are accompanied by increased risk for cardiovascular disease. These risk factors are atherogenic dyslipidemia, elevated BP, elevated plasma glucose, a prothrombotic state, and a proinflammatory state.[21, 22] Each abnormality promotes atherosclerosis independently, but when clustered together, these metabolic disorders are increasingly atherogenic and enhance the risk of the development of CAD and cardiovascular events.[2, 3, 23] Currently MS is a term used to define a patient who presents with three or more of the five defined risk factors: hypertriglyceridemia, low HDL cholesterol, fasting hyperglycemia, abdominal obesity and hypertension.[12, 21]

The MS has been shown to affect at least 20% of the U.S. adult population, and its prevalence has been shown to increase in older patients and in certain ethnic groups.[24] This prevalence increases dramatically in patients with CAD, and the MS has been linked to an increased incidence of cardiovascular disease and cardiovascular morbidity and mortality.[21, 25] Solymoss et al. found that MS cased on the ATP III definition, was present in as many as 51% of patients with documented CAD.[26] Lakka et al. reported on results of the Ischemic Heart Disease Risk Factor Study, a prospective study of 1,209 Finnish men aged 42-60 years at baseline who were initially without cardiovascular disease, cancer or diabetes. After adjustment for conventional risk factors, men with MS were 3.8 times more likely to die from coronary heart disease, 3.6 times more likely to die of any cardiovascular disease, and 2.4 times more likely to die from any cause.[21]

From the clinical and public health perspective, it has been questioned whether MS improves cardiovascular risk prediction, beyond previously used tools such as FRS for CAD.[14, 27-30] In some study, MS was less effective at predicting CAD than the FRS, because prediction criteria based on MS alone

do not include several well established risk factors for CAD such as serum total cholesterol level and smoking habitus.[29, 30] In a recent study, however, the MS may help predict an increased cardiovascular risk beyond that predicted by the more frequently used tool FRS. In our study, MS was effective at predicting CAD as well as FRS.

The association between the MS score and Gensini score that was observed in the present study may imply a strong association between MS and CAD.[31, 32] Gensini score was significantly higher in MS positive than in MS negative patients. Conversely, normal coronary arteries were more frequent in MS negative patients. Concerning the magnitude of these differences, MS negative patients have their own coronary risk factors. Even though in the presence of less than three constituents patients did not fulfill the newly defined diagnostic criteria of MS, one or two constituents can promote coronary atherosclerosis.[26]

Another central issue from the epidemiological perspective is whether the MS predicts cardiovascular disease above and beyond its individual components.[33] In a 13-year follow-up study in elderly non-diabetic Finnish population, impaired fasting glucose, impaired glucose tolerance, low HDL cholesterol, and microalbuminuria predicted CVD mortality with equal or higher hazard ratios when compared with the MS. Therefore, the MS is a marker of CVD risk, but not above and beyond the risk associated with its individual components.[33, 34] In the present study, increased FBG was only the most powerful predictor of outcome nevertheless increased BP, decreased HDL and increased BMI were the three most frequently observed characteristics. Interestingly 33% of normoglycemic individuals also had MS, indicating that during the evolution of insulin resistance, abdominal obesity, high triglycerides and low HDL cholesterol type dyslipidemia, as well as hypertension, frequently precede increased blood glucose level.

The analysis of the 11 possible combinations hidden in the unspecified diagnosis overall MS reveals a striking heterogeneity in their ORs as CAD

risk factors. As shown in table 4, the ORs of these 11 phenotypes vary in a wide range from 1.358 to 3.731 depending on individual components. The cluster of the MS including high FBG, high BP and low HDL are clearly associated with the highest CAD risk showing OR 3.731. On the other hand some clusters revealed ORs below average risk. This was the case for specified phenotypes if they did not include high BP and low HDL as components. Our investigation demonstrates that the CAD risk strongly depends on the individual components.

The present study shares the limitations of nonrandomized, retrospective studies, including the possibility of selection bias and uncorrected confounding. The generalizability of the results is limited by the racial and ethnic background.

No agreement exists as to the definition of the MS diagnostic criteria. We have chosen to study only the NCEP ATP III criteria for definition of the MS because the ATP III considered the association between MS and cardiovascular risk as the founding characteristics of the syndrome. This definition was designed for clinical use, and our study was designed to provide practical answers.[2, 3]

Although the NCEP noted that the MS is characterized by a prothrombotic and proinflammatory state, the diagnostic criteria do not reflect these components of the syndrome.[3] Ridker et al reported on the prognostic importance of features of the MS and the inflammatory marker C-reactive protein(CRP) in 14,719 previously healthy women in the Women's Health Study who were followed for an average of 8 years. Risk increased with increasing numbers of MS features, and at each level of MS risk, elevated CRP added to risk.[25] However it has been shown in a recent study that CRP was not associated with the extension or complexity of CAD,[35] and our finding is consistent with those of recent study.

While being overweight and obesity are associated with insulin resistance and MS, the presence of abdominal obesity is more highly correlated with

metabolic risk factors than is BMI. Thus the simple measurement of waist circumference, with sex specific thresholds, was recommended by ATP III to identify the body weight component of MS.[2, 3] However, because waist circumference was not available, we used a BMI of about 25 kg/m^2 which has been applied as a surrogate in a report of prevalence of obesity and MS in Korean adults.[16]

The biochemical diagnosis of insulin resistance requires the euglycemic clamp techniques, which is useful for basic research but impractical for clinical or epidemiologic investigation. Fasting insulin levels correlate reasonably well with the degree of insulin resistance.[36]

V. CONCLUSION

In our study, MS was associated with the presence of angiographic CAD, and this predictive ability of MS was carried almost entirely by high FBG. Additionally individual traits in some clusters with high BP and low HDL may act synergically as risk factors. Thus, fasting glucose deserve particular attention in risk factor assessment and prevention in subjects at risk for CAD. The strong and consistent association of dysglycemia with cardiovascular risk demonstrated in this study adds to evidence from multiple other studies. Particularly attention should be paid to preventing and treating diabetes.

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ABSTRACT (IN KOREAN)

관상동맥 질환의 중증도와 대사 증후군 위험인자 집적도의 상관관계

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문 희 선

대사 증후군은 조기 죽상 동맥경화의 발생과 진행에 관련된 여러가지 대사 이상이 동시에 발생하는 것이다. 이에 대사 증후군이 있는 환자군과 없는 환자군 간에 임상적인 여러가지 지표를 비교하고 대사 증후군 5 가지 각각의 위험인자 집적도와 관상동맥 조영술상의 중증도 사이에 어떤 관계가 있는지 평가하고자 하였다. 그리고 대사 증후군과 각 구성 요소들, 그리고 여러가지 조합을 통해서 관상동맥 질환을 진단하는데 있어서의 예측도를 비교하고자 하였다. National Cholesterol Education Program Adult Treatment Panel III 진단 기준에 의거하여 대사 증후군을 정의하였으며 관상동맥 질환의 중증도는 Gensini 점수화 체계를 이용하여 평가하였다. 대사 증후군이 있는 군과 없는 군 간에 몸무게, 체질량지수, 혈압, 당대사와 지질대사 이상을 나타내는 표지자들과 몇몇 생화학적인 지표들에서 통계학적으로 유의미한 차이가 있었다. 대사 증후군 위험인자의 집적도와 Gensini 점수는 양의 상관관계가 있었고 이로써 관상동맥 질환의 중증도가 심해짐을 알 수 있었다. 높은 공복혈당은 가장 강력한 예측인자이며 고혈압과 낮은 고밀도 지단백 콜레스테롤을 동반한 조합에서는 위험인자로서의 상승효과가 나타났다.

핵심되는 말 : 대사 증후군, 관상동맥 질환