Metabolic syndrome and Severity of coronary artery disease in west of Iran

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Abstract: CAD is cause of half of the total death in Iran and metabolic syndrome (MS) is considered as a high prevalent risk factor of CAD. This case-control survey aimed to investigate the relationships between MS and lifestyle risk factors with coronary artery disease in patients with and without CAD undergoing angiography in Kermanshah Heart Center, West Iran. Metabolic syndrome criteria were based on National Cholesterol Education Program/ Adult Treatment Panel, modified by American Heart Association / National Heart Lung & Blood Institute in 2005.Quantitative data analysis techniques including paired samples t-test, conditional logistic regression (to quantify the Odds Ratio), chi-square, and multivariate modeling (to assess the effects of metabolic syndrome with and without adjustments) were done. Almost all of the MS components were linked with risk factors of CAD and at least one MS component was present in all CAD patients. MS with all of five components increased the risk of CAD significantly more than thirteen times; additionally MS with minimum of three components increased the risk significantly more than four times. low HDL-c and high FBS were positively and significantly related to first grade of CAD severity. It was found that low HDL-C, high BP and high FBS were significantly more likely to occur in grade-II CAD-severity. Almost all of the MS components except WC were significantly and positively related to severe (grade III) CAD. Furthermore most of the patients with CAD had multi-vessel stenosis (grade III) which was the severest level of CAD, suggesting that CAD was often diagnosed when stenosis developed severely which remarkably decreases the chances of successful treatment. Implications of these findings are useful for clinical practices as well as for general health practices. The results clearly show that early diagnosis of most MS components could delay or even is likely to deter the development of CAD in lower grades of CAD severity.

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1. Introduction

Coronary Artery Disease (CAD) also known as Coronary Heart disease (CHD) is a term which refers to narrowing of the small blood vessels that supply blood and oxygen to the heart. It usually shows itself in the form of myocardial infarction (MI) or ischemic heart disease (IHD).The term CHD applies to situations where impaired blood flow in the coronary arteries results in angina, myocardial infarction, and sudden death. CAD is the most common form of cardiovascular diseases as a result of arteriosclerosis and arteriosclerosis and is known as a chronic and systemic disease of the entire arterial system. Previous research shows that the cardiovascular disease (CVD) has been the leading cause of death in the world for more than 100 years. Although most of the deaths from CVD occur in elderly people (usually above 65) one third of these deaths occur sooner. The high death rate of CVD made the researchers to do extensive research on its prevention. There are several epidemiologic studies as well as experimental studies (clinical or community trials) that have delineated the risk factors associated with CVD development. The preventive measures based on the above studies resulted in one of the greatest public health successes in the last century which was the significant decrease in age-adjusted mortality rates from CVD (Thom et al., 2006).

Metabolic Syndrome (MS) also known as syndrome X, is comprised of hypertension, glucose intolerance, high triglycerides, and decreased level of high density lipoproteins (HDL). These defects in the body are considered as risk factors of cardiovascular diseases (Reaven, 1988). MS is also at time referred to as the Deadly Quartet, the Dysmetabolic Syndrome, and Insulin Resistance Syndrome. The above mentioned MS risk factors are considered as the main causes of development and progression of atherosclerosis, which eventually results in a higher risk for coronary artery diseases. MS components have also been associated with a higher risk for diabetes type 2. Generally, there is no single cause for MS;

however, abdominal obesity and insulin resistance are the most important risk factors for this disease. Other underlying risk factors that can increase the risk of MS include physical inactivity, aging, hormonal imbalance, and race (Grundy, 2005). The results of these studies have shown that patients with MS have a higher risk of developing CVD mortality & morbidity (Isoma et al. 2001, Chen et al., 2008). The main reason for this association is that a combination of risk factors concomitant with MS interacts synergistically with several other factors thereby causing or accelerating the progression of atherosclerosis (Isoma et al., 2002). It has been found that individuals with one or two of the MS components are at a two-fold greater risk of CAD and CAD mortality (Gorter, 2004; MacNeill et al., 2004). Similar studies have shown that the coronary artery disease is the leading cause of death in general population in Iran (Azizi et al., 2004).

Although a strong link between MS and coronary artery disease (CAD) has not been well documented (Petra et al., 2004); studies investigating MS (Maki et al., 2004; Lee et al., 2005; Niaura et al., 2000; Raikkonen et al., 2002) have shown that MS can be influenced by biological, behavioral, and social factors which have already been identified as factors affecting the development of CAD. Likewise, The results of a few studies conducted on prevalence of MS and its risk factors in general population in Iran (Zabetian et al., 2007) have suggested that MS factors can trigger CAD development although there is little knowledge determination of risk factors of MS in high risk patents in Iran. Zabetian et al. (2007) notes that over the past years general population in Iran have experienced rapid life style changes with drastic reductions in physical activity and increase in consumption of processed food, resulting in an epidemic of obesity and diabetes. The results of these studies indicate that lifestyle changes and dietary habits that carry the risk of MS, can also lead to aggravation of CAD patients' condition; however, research on life style screening for MS risk factors in CAD patients in the setting of this study-Iran has been scarce.

Review of the literature on metabolic syndrome demonstrates that MS is a prevalent syndrome both throughout the world and in Iran. The noteworthiness of the epidemiologic studies on MS in Iran is that the prevalence of this syndrome is considerably higher in this region than the world rate. As a result of the combined effect of risk factors of MS, we know that the prevalence of MS is increasing parallel to the trend in overweight and obesity (Azizi et al., 2004). Generally, the prevalence of MS increases with age and its prevalence are considerably different among races and ethnic groups, which supports the probable impact of genetic predisposition. Based on the reviewed literature, it becomes evident that the genetic factors as well as the social, environmental, psychological, and behavioral variable are linked to this clinical syndrome to some extent although the direct association of these factors with CAD is still in need of further research. Previous studies (Azizi et al., 2004; Zabetian et al., 2007) have recommended a strong need for more studies to explain the interrelation between MS components and their association with CAD.

Severity of CAD is assessed in two ways. First, by the number of vessels (0–3) with at least one significant stenosis (50% stenosis), Second, by the Gensini scoring system that is used to calculate coronary disease severity (Chen et al., 2007). This method defines narrowing of the lumen of the coronary arteries as 1 for 1-25% stenosis, for 26-50% stenosis, 4 for 51-75% stenosis, 8 for 76-90% stenosis, 16 for 91-99%, and 32 for total occlusion. The score is then multiplied by a factor that represents the importance of the lesion's location in the coronary artery system. In the present study the first method was used. Several studies (Chen et al., 2007) assessing the severity of CAD and MS have shown significant relationships between these two clinical entities; however, some other studies have shown no significant relationship between the number of vessels and metabolic syndrome (Ertek et al., 2011). Hence, the association of MS diagnostic criteria with current vascular disease severity warrants further investigation. Ertek et al. (2011) discuss that the presence of MS does not seem to be associated with more frequent severe coronary lesions, probably because of some other factors contributing to coronary risks.

2. Materials and Methods

A Case Control study design was undertaken to determine the association between Metabolic Syndrome and other risk factors of CAD with Coronary Artery Disease in patients with and without CAD undergoing angiography in Kermanshah Heart Center, West Iran.

The study population included adults aged over 45 who had been admitted to Imam Ali Heart Center in Kermanshah, west Iran for angiography during the data collection for this study were invited to participate in this study with informed consent statement. The sampling method was of a systematic sampling for Cases. The control group was selected based on matching for sex and age (±3 years) of the cases.

Based on the sample size calculation (confidence interval 95%, Power 80%, P0=0 and P1=0.025), a minimum of 624 patients (312 cases, 312 controls) proved as the required sample size for the

present study. A total of 3000 patients undergoing the angiography were initially surveyed. To ensure maximum reliability and validity of the provided input two main sources of systematic error; that is, selection and bias recall were taken into consideration. In order to eliminate selection bias, objective criteria both for patients and healthy controls were set.

2.1. Metabolic Syndrome Assessment

The National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP) has introduced one of the most widely accepted diagnostic criteria for the diagnosis of MS. This criteria works on some measurements including waist circumference, serum triglyceride (TG), HDL-C, Blood pressure (BP), and fasting blood sugar (FBS). Recently, the American Heart Association/National Heart Lung & Blood Institute (AHA/NHLBI) has made some minor modifications on the NECP criteria which is currently used in research focusing on MS and its association with Coronary Artery Diseases (CAD) (Grundy, 2005).

1. Waist circumference > 88 cm
2. Fasting triglycerides ≥ 150 mg/dL or medication for treatment
3. HDL cholesterol < 50 mg/dL or medication for treatment
4. Hypertension (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg or medication for treatment
5. Fasting glucose ≥ 100 mg/dL or medication for treatment

2.2. Assessment of CAD and Severity of CAD

The elective coronary angiography was performed using Judkin's approach. CAD was defined as > 50% luminal diameter stenosis of at least one major epicardial coronary artery. Patients were divided into four subgroups according to the anatomy of coronary vessel lesions as revealed by the coronary angiography test: (i) normal group, (ii) single-vessel group, (iii) two-vessel group and (iv) multivessel group (the number of blocked coronary vessels over 2). The presence of CAD was determined in the right coronary, the left anterior descending and left circumflex coronary artery. If the left coronary artery main stem was involved, the patient belonged to the two-vessel group.

2.3. Data analysis

All statistical analyses were performed using SPSS version 18 and STATA11. Descriptive statistics such as frequencies, percentages, means, ranges and standard deviations were used to describe the data. The Coronary artery disease was considered as the dependent variable, while all other variables were analyzed as independent variables. After checking for normality, for normally distributed continuous variables Paired Samples t-test was used to determine the differences between the case and control groups. For non-normally distributed continuous variables, the Wilcoxton matched pairs signed rank test was used. McNemar's test (sometimes called McNemar's test of symmetry or McNemar symmetry chi-square) was used to determine the association between categorical variables with the CAD. $p < 0.05$ was used as level of significance.

Conditional logistic regression was then applied to quantify the relative odds of CAD associated with MS and its components and other life style risk factors of CAD (The Mantel-Haenszel test could be assessed in the normal stratified analysis method but with the many strata, stratification produces sparse data the CLR algorithm is designed to handle sparse data). Correlation between each of MS components and each of CAD-severity grades have done by Multinomial logistic regression.

3. Results

The intent of the forth research question was to assess the relationship between the severity of CAD and MS.

3.1. Severity of CAD in Cases

Table 1 shows the frequency distribution of CAD severity among the patients. Patients were divided into four subgroups according to the anatomy of coronary vessel lesions as revealed by the coronary angiography test: (i) normal group, (ii) single-vessel group or grade I, (iii) two-vessel group or grade II and (iv) multivessel group (the number of blocked coronary vessels over 2) or grade III. If the left coronary artery main stem was involved, the patient belonged to the two-vessel group. Severity of CAD in 67(22.7%) of the cases fell under the first level (Grade I). Seventy seven (26.1%) of the cases could be categorized as grade II-CAD severity patients and 151(51.2%) of them were found to belong to the grade III, having problems in more than two of the heart vessels. The most frequent severity was seen among grade III patients.

Table 1. Severity of CAD in Cases (N=295)

CAD-Severity Level	n	%
Single vessel (Grade I)	67	22.7
Two vessels (Grade II)	77	26.1
Multivessels (Grade III)	151	51.2
Total	295	

3.2. MS and CAD Severity

Table 2 shows the frequency distribution of CAD severity and MS with 3, 4 and 5 Components. most of the CAD patients (87.45%) have MS and

about half of CAD-MS patient are in grade 3 of CAD and it means they had sever CAD.

Table 2. CAD Severity among Patients with 3, 4 and 5 MS Components (N=295)

MS category	CAD Severity (*n*, %)			
	Grade I	**Grade II**	**Grade III**	**Total MS**
3 components	15(5.08)	19(6.44)	37(12.54)	71(24.06)
4 components	23(7.79)	32(10.84)	52(17.62)	107(36.27)
5 components	22(7.45)	16(5.40)	42(14.48)	80(27.11)
MS	60(20.62)	67(22.68)	131(44.64)	258(87.45)
				Total Non-MS
Non-MS	7(2.37)	10(3.38)	20(6.77)	37(12.54)
Total CAD	67(22.71)	77(26.10)	151(51.18)	

Table 3. Correlation between MS and CAD Severity

			CAD Severity	**Ordinal_MS**
Spearman's rho	CAD severity	Correlation Coefficient	1.00	-0.03
		Sig. (2-tailed)	.	0.58
		N	297	295
	Ordinal_MS	Correlation Coefficient	-.03	1.00
		Sig. (2-tailed)	0.58	.
		N	295	295

As table 3 shows, the results of correlations between MS with 3, 4 and 5 components and CAD severity across different grades by Spearman's rho correlation analyses shows that there was no significant correlation between CAD-severity and MS (3, 4, 5 components), (r=-0.032, n=295, p=0.58).

Our findings show the correlation between each of MS components and each grade of CAD severity. This analyze done by multinomial logistic regression, reference group for comparison was normal group (non-CAD). The results shows that patients that had low HDL-C or used medication for that had normal HDL-C, were more likely to be in grade - one CAD severity in compare to be non-CAD (OR=4.82 ,95%CI=2.16-10.72, P= 0.00). Similarly, patients that had elevated FBS or used medication for that in comparison normal-FBS-patients, were more likely to be in grade-one CAD (OR=2.54 ,95%CI=1.43-4.50, P=0.00). The results also showed that patients that had low HDL-C or used medication for that in compare to patients that had normal HDL-C, were more likely to be in grade-II CAD-severity in compare to be non-CAD (OR= 2.14, 95 % CI=1.16-3.94 , P=0.01). The results shows that patients that had elevated FBS or used medication for that in compare to patients that had normal FBS, were more likely to be in grade-II CAD-severity in compare to be non-CAD (OR=1.90 ,95% CI=1.12-3.20 , P=0.01). In addition, the results shows that patients that had elevated BP or used medication for that in compare to patients that had normal BP, were more likely to be in grade-II CAD-severity in compare to be non-CAD (OR=3.01 , 95% CI=1.23-7.37, P=0.01). We also found that patients that had elevated TG or used medication for that in compare to patients that had normal TG, were more likely to be in grade-III CAD-severity in compare to be non-CAD (OR= 2.04, 95%CI=1.22-3.43 , P=0.00).

The results shows that patients that had decreased HDL-C or used medication for that in compare to patients that had normal HDL-C, were more likely to be in grade-III CAD-severity in compare to be non-CAD (OR=1.98 , 95%CI=1.23-3.19, P=0.00). The results shows that patients that had elevated FBS or used medication for that in compare to patients that had normal FBS, were more likely to be in grade-III CAD-severity in compare to be non-CAD (OR=2.18 , 95%CI=1.43-3, 32 , P=0.00). The results shows that patients that had elevated BP or used medication for that in compare to patients that had normal BP, were more likely to be in grade-III CAD-severity in compare to be non-CAD (OR=2.70 , 95%CI=1.40-5.21 , P=0.00).

4. Discussions

Severity of CAD is often defined on the basis of classifying CAD patients into four groups according to the anatomy of coronary vessel lesions as determined by the coronary angiography test: (i) normal, (ii) single-vessel or grade I, (iii) two-vessel group or grade II and (iv) multi vessel group (the number of blocked coronary vessels over 2 known as grade III (Chen et al., 2008). Coronary angiography test results revealed that severity of CAD in 67(22.7%) of the cases fell under the first level (Grade I). Seventy seven (26.1%) of the cases were categorized as Grade II patients and 151(51.2%) of them were identified to belong to Grade III, which indicated patients having problems in three of the heart vessels. It was notable that the most frequent severity of CAD was seen among grade III patients. This can also show that most of CAD patients are diagnosed in latest stages of CAD development after it has already developed into severer stages. Therefore, the results imply a partial weakness in early diagnosis of the disease, either by the medical institutions in the society or as a result of the lack of information with respect to its initial signs of development. Hence, the result of inaction in early diagnosis and treatment of CAD, which is much easier and has higher chances of prevention, can lead to the severity in this deficit in the body and eventually bring about increased morbidity of the disease.

Although research on severity of CAD among MS patients has received scant attention by the existing body of research, among the limited number of studies in this respect indications of a close relationship between these two clinical phenomena have been pointed out. Analysis of the current data showed that most of the CAD patients (87.45%) also suffer from MS symptoms and about half of CAD-MS patient are in grade III of CAD severity, suggesting the most advanced level of involvement with CAD. Only 37(12.54%) out of 295 participants were identified as Non-MS Patients. Grade III CAD severity was also prominent among Non-MS CAD patients (6.77%, n=20).

These results are in line with Chen et al.'s (2006) study which aimed at investigating the relationship between MS and severity of CAD. Chen et al. (2006) found that the prevalence of MS in CAD group was significantly higher as compared to the groups not suffering from CAD ($p < 0.01$). The CAD–MS group showed a higher prevalence of multi vessel disease ($p < 0.05$), results of coronary angiography in the CAD patients with or without MS, showing that single-vessel disease in the CAD group was more frequent (62.5%, $p < 0.01$), while three-vessel disease in the CAD–MS group was more common. Using the Julkins approach. It is worth noting that the study used Julkins approach (used by previous research such as Chen et al., 2006). In Chen et al. (2006) the CAD was defined as a 50% narrowing of the luminal diameter in one or more major epicardial arteries or their major branches heart disease (CAD) in aged patients. In this study, the classification of 125 aged patients after coronary angiography and evaluation by WHO and NCEP criteria included 40 patients with CAD (32%), 38 with CAD–MS (30%), 11 with MS (9%), and other 36 patients belonged to the control group (29%). The results showed that the cumulated occurrence of MS symptoms was significantly higher in the CAD group than in the non-CAD group (48.7% versus 23.4%, $p < 0.01$). The study also reports that in CAD group the value of BMI, prevalence of hypertension and hyperglycemia were higher than those of the non-CAD group ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively) whereas TG and HDL-C did not differ significantly between two groups. Moreover, Chen et al. (2006) found that the prevalence of MS in CAD group was significantly higher as compared to the groups not suffering from CAD ($p < 0.01$). The CAD–MS group showed a higher prevalence of multi vessel disease ($p < 0.05$), results of coronary angiography in the CAD patients with or without MS, showing that single-vessel disease in the CAD group was more frequent (62.5%, $p < 0.01$), while three-vessel disease in the CAD–MS group was more common.

he results of correlations between different categories of MS (i.e., MS with 3, 4 and 5 components) and CAD severity across different grades of CAD severity as determined by Spearman's rho correlation analyses indicated no significant correlation between CAD-severity and the total MS components ($r=-0.032$, $n=295$, $p=0.58$). However, the correlation between individual MS components and each grade of CAD severity determined by multinomial logistic regression (reference group for comparison was normal group or non-CAD) showed significant correlations between these variables.

The results also show that patients with decreased HDL-C, elevated FB or took medication for these diseases were more likely to be in grade I or III of CAD severity in comparison to patients that had normal HDL-C. (OR=4.82, 95%CI=2.16-10.72, P= 0.00.) It was also noted that patients that with elevated BP and TG or those who used medication for these, were more likely to be in grade-II CAD severity to non-CAD in comparison to patients that had normal BP and TG. These results could be so important to prevent severe cardiovascular pathologies in MS patients, and also for prediction of severity of coronary lesions in MS patients during clinical practice.

Several studies have evaluated the association between CAD severity and different components of MS, however, these studies have not explicitly referred to the correlations between each individual grade of CAD severity and MS or its components. For instance, Ertek et al. (2010) in a study of cohort of Turkish patients undergoing elective coronary angiography investigated the relationship between metabolic syndrome (MS) and the severity of coronary lesions in a sample of diabetic and non-diabetic patients undergoing elective coronary angiography. The study reports that neither any one of MS components nor did gender reveal significant relationship with coronary disease severity. In a similar trial, Jong-Youn et al (2010) examined 632 patients who underwent coronary angiography for suspected CAD. About seventy-eight percent (n=497 of the patients had CAD and 283 (44.8%) were diagnosed with MS. The MS score was significantly related to the Gensini score. The study also showed that high fasting blood glucose (FBG) was the only predictive factor for CAD. In other words, the study concludes that the predictive ability of MS for CAD was carried almost completely by high FBG. Moreover, individual traits with high BP and low HDLC may act synergistically as risk factors for CAD as increasing MS score has been reported to be significantly related to the severity of CAD on the coronary angiography (Jong-Youn et al., 2010). Indeed, as Jong-Youn et al. (2010) assert that, patients with and without MS did not differ in the prevalence

of CAD and diseased vessel numbers, however, patients with MS had severer CAD compared to patients without MS as assessed by the Gensini score.

In a similar trial, Hsieh et al. (2009) studied a total of 148 patients with at least one side of the extra cranial internal carotid artery. The results revealed that the MS score and total plasma homocysteine level were significantly correlated with affected vessel number in CAD and the extent of coronary atherosclerosis. Hsieh et al. (2009) also note that MS can predict the presence of CAD in patients with carotid stenosis. Likewise, Zornitzk et al. (2007) who evaluated risk factors for CAD in women and their association with the severity and extent of coronary angiographic findings. The location and extent of coronary artery occlusions were assessed using the modified Gensini index. They found that diabetes, fasting plasma glucose and hypertension, but not the metabolic syndrome, were associated with severity of coronary angiographic findings in these women. Some of main findings of Zornitzk et al.'s (2007) study were identifying diabetes and increased FBG as risk factors for more severe CAD in women. Furthermore, the authors maintain that diabetes and hypertension were both independent predictors of coronary artery disease severity. It was also noted that although metabolic syndrome was more prevalent in women with CAD than in the NCAD group, it was neither an independent predictor of CAD nor of coronary angiography findings (Ganjigatte V, 2011; Patel M., 2011; Yathish TR, 2010; Zornitzki et al., 2007).

To sum, the analysis of the data on the association of CAD severity with different categories of MS (i.e., Grade I, II, and III), discussed earlier, consistent with the previous research confirms the fact that the prevalence of MS among CAD patients is considerably high. Having said this, the results show that patient with higher grades of CAD severity are more vulnerable to be contracted with MS in comparison to those who are struggling with less severe (lower grades) of CAD. In conclusion, most of CAD patients have multi vessel (grade III) or sever CAD, suggesting that CAD is often diagnosed at later ages of development and severity, which remarkably decreases the chances of successful treatment.HDL and FBS are related to all type of CAD severity.

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