

Comparison of cardiovascular risk factors and biochemical profile in patients with cardiac syndrome X and obstructive coronary artery disease: A propensity score-matched study

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Original Article

Abstract

BACKGROUND: This study was designed to compare the frequency of conventional cardiovascular disease risk factors and clinical biochemistry profile in patients with cardiac syndrome X (CSX) and obstructive coronary artery disease (CAD).

METHODS: A cross-sectional study was conducted on patients with typical angina and positive exercise tolerance test undergoing coronary angiography in our center. 342 consecutive patients with CSX were enrolled into this study and were matched regarding age and sex with 342 patients with acute coronary syndrome (ACS) and also 342 patients with chronic stable angina (SA). Cardiovascular risk factors as well as biochemistry profile of the patients were recorded.

RESULTS: Mean age of the studied patients was 53.0 years and 41.5% were male. There was no significant difference between the CSX patients and CAD patients regarding body mass index (BMI). Frequency of diabetes mellitus, hyperlipidemia, smoking, family history of premature CAD and hypertension was significantly lower in patients with CSX than ACS and SA patients. Patients with CSX had significantly higher levels of high-density lipoprotein cholesterol (HDL-cholesterol) than comparators while the levels of low-density lipoprotein cholesterol (LDL-cholesterol), total cholesterol, triglyceride and fasting blood sugar (FBS) were significantly lower in patients with CSX than CAD patients.

CONCLUSION: The present study demonstrated that CSX patients had substantially lower frequency of all conventional CVD risk factors than patients with obstructive CAD. This might aid in developing novel scoring systems or appropriateness criteria for angiographic evaluation of patients with typical angina and positive exercise test in order to reduce the rate of negative results.

Keywords: Cardiac Syndrome X, Microvascular Dysfunction, Coronary Artery Disease, Risk Factors

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Introduction

Cardiac syndrome X (CSX) is defined as typical angina pectoris and normal or near normal coronary arteries at angiography; however, ST segment depression during exercise stress test is also included in the modified definitions of CSX.¹⁻⁴ Regardless of low mortality, patients with CSX have high morbidity and health care expenditure comparable to patients with obstructive coronary artery disease (CAD).^{5,6} In fact, because of the refractory nature of the chest

pain, a significant functional disability may remain in many of these patients, often women, and represents a considerable burden on hospital resources, as these patients continue to use hospital facilities, including emergency and coronary care beds.⁵

CSX is associated with a wide range of clinical characteristics which may reflect differences in etiology and outcome. Several pathophysiologic mechanisms have been suggested for that; inflammation, endothelial dysfunction (ED),

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impaired pain perception, and insulin resistance are among the suggested etiologies of CSX.⁷ A major diagnostic challenge for the cardiologist, however, is whether patients with CSX can be distinguished with sufficient validity and reliability from those with obstructive CAD on the basis of a careful assessment of clinical characteristics and non-invasive investigations. This would avoid subjecting the patient to the small but definite risk associated with coronary angiography, which would have favorable effects on healthcare costs and allow better utilization of medical resources.⁸ Thus, this study was designed to compare the frequency of conventional CVD risk factors between the patients with angiographically determined obstructive CAD and patients with CSX. The results of this study might be a substrate for clinical differentiation of CSX and CAD and for more comprehensive planning for diagnostic tests.

Materials and Methods

Study Population

A retrospective cross-sectional study was performed in this study. Between May 2009 and May 2010, 373 patients with typical angina and a positive exercise test were enrolled in the study who underwent diagnostic coronary angiography at cardiac catheterization laboratory of Tehran Heart Center (affiliated to Tehran University of Medical Sciences) and found to have normal coronary angiograms. After excluding 41 patients with valvular heart disease, left ventricle hypertrophy, cardiomyopathy, left ventricular ejection fraction (LVEF) \leq 50%, congestive heart failure and a positive history of coronary spasm, 342 remaining patients were considered for the final analysis. In addition, there were 2031 patients with ACS and 2470 patients with chronic stable angina (SA) who underwent coronary angiography at the same time period who were used as a pool of potential comparators. In fact, as there was evidence that patients with CSX were more likely to be female and to have lower ages and on the other hand conventional risk factors of CVD were more likely to be present in males and older ages, it was decided to eliminate the potential confounding effects of age and gender through matching for more clarification of the difference of the CSX and CAD patients regarding their risk factors. Hence, propensity scores were used to match the 342 CSX patients with 342 ACS and 342 SA matched comparators for age and sex in a 1: 1 fashion.

Study Protocol

Demographic data including sex, age, weight, body

mass index (BMI), hypertension, hyperlipidemia, DM, smoking, and family history of CAD, in addition with the results of biochemical examinations including fasting blood glucose and lipid profile were recorded and analyzed. Medication history of the patients in each group was also recorded and compared with together. The study protocol was reviewed and accepted by the Ethics Committees of Tehran University of Medical Sciences and Tehran Heart Center (Approval date: 2008-11-08, approval number: 89/210/7962) and verbal informed consent was obtained from all the patients. Investigators guaranteed to use the medical documents of the study participants confidentially and not to impose any research-related charge to them.

Laboratory Assays

Peripheral venous blood specimens were collected from an antecubital vein after 10-12 fasting hour of the subjects. Fasting plasma glucose (FPG) was measured by the glucose-oxidation method (Pars Azmoon, Tehran, Iran) and total cholesterol (TC), triglyceride (TG), and low density lipoprotein-cholesterol (LDL-C) were determined by enzyme colorimetric assay (Pars Azmoon, Tehran, Iran) using a Hitachi autoanalyzer (type 717, Hitachi medico, Tokyo, Japan). High density lipoprotein-cholesterol (HDL-C) was measured using precipitation-based method. All measurements were performed in Tehran Heart Center laboratory with adherence to external quality control.

Definitions

Cardiac syndrome X was defined as coexistence of typical angina pectoris, positive exercise stress test (ST segment depression during stress test) and normal coronary angiogram.⁴ CAD was defined as \geq 50% luminal diameter stenosis in one or more major epicardial vessel and included patients with ACS and SA.^{9,10} ACS consists of ST elevation myocardial infarction, non ST elevation myocardial infarction and unstable angina. Angina pectoris and associated CAD symptoms precipitated by activity with minimal or non-existent symptoms at rest, were defined as SA.¹¹

Risk factors including smoking, DM, hypertension, hyperlipidemia, and family history of premature CAD were defined on the strength of standard definitions.¹²⁻¹⁵ Patients who consumed opium by any route (inhalation or oral) were considered as opium-users.¹⁶

Statistical Analysis and Propensity Score Matching

A propensity score-matching methodology was applied to identify comparator groups who were statistically equivalent based on age and gender.¹⁷

Using nearest available Mahalanobis metric matching within calipers defined by the propensity score, each CSX patient with an ACS patient and a SA patient whose propensity scores were closest were adjusted.¹⁸ The Kolmogorov-Smirnov test was applied to examine normal distribution. Continuous variables were expressed as mean \pm SD and were compared among three groups of patients by analysis of variance (ANOVA) followed by Scheffe's post-hoc test for pairwise comparisons. Categorical variables were compared using a chi-square test or Fischer's exact test as appropriate, and were presented as absolute frequencies with percentages. All P values were two-tailed with significance defined as $p \leq 0.05$. For the statistical analysis, the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) was used.

Results

Clinical characteristics of the patients in three groups are presented in table 1. Mean age of the study subjects was 53 years and 426 of them (41.5%) were male. There was no significant difference between CSX patients and ACS patients and also between CSX and SA patients with respect to BMI. Frequency of diabetes mellitus was significantly smaller in patients with CSX (15.6%) than ACS (37.0%) and SA (32.8%) patients (P for both comparisons < 0.0001). Similar to diabetes

mellitus, the prevalence of hyperlipidemia was also significantly lower in CSX group (16.4%) than ACS (36.8%) and SA (32.7%) groups. While patients with SA were more likely to be hypertensive than CSX patients (190 vs. 138, respectively), there was no significant difference between CSX and ACS groups regarding the prevalence of hypertension. ACS and SA groups were also more likely to have a positive family history of premature CAD as compared to CSX group (P for both comparisons < 0.0001). The frequency of current smoking was significantly lower in patients with CSX (36) than ACS (84) and SA groups (58). Although the opium abuse was more frequent in ACS group than CSX group (52 vs. 22, respectively, $P = 0.001$), the prevalence of opium abuse was similar in CSX and SA groups.

Table 2 demonstrates the plasma biochemistry profile of the participants. Plasma concentrations of HDL-C was significantly higher in patients with CSX compared to ACS and SA groups ($P = 0.001$ and $P = 0.026$, respectively). Although the comparison of LDL-C levels did not show a statistically significant difference between ACS and XSC groups ($P = 0.076$), patients with SA had a significantly higher concentrations of LDL-C than CSX patients (124.6 mg/dl vs. 115.3 mg/dl, respectively; $P = 0.009$). Serum levels of TC, TG and FPG were also significantly higher in ACS and SA groups compared to CSX group (P for all comparisons < 0.0001).

Table 1. Baseline clinical characteristics of the study subjects

	ACS (n = 342)	SA (n = 342)	CSX (n = 342)	P ACS vs. SA	P CSX vs. SA	P CSX vs. ACS
Age (yr)	53.0 \pm 8.5	53.0 \pm 8.3	52.9 \pm 8.6	0.993	0.817	0.8120
Male sex, n (%)	142 (41.5)	141 (41.2)	143(41.8)	0.999	0.938	0.9990
BMI (Kg/m ²)	28.1 \pm 4.9	29.0 \pm 4.7	28.5 \pm 4.4	0.010	0.134	0.2490
CV risk factors, n (%)						
Diabetes mellitus	126 (37.0)	112 (32.8)	53(15.6)	0.296	< 0.0001	< 0.0001
Hyperlipidemia	263 (77.8)	268 (78.4)	211 (62.2)	0.926	< 0.0001	< 0.0001
Hypertension	162 (47.4)	190 (55.9)	138 (40.6)	0.027	< 0.0001	0.0770
Family history	136 (41.0)	111 (32.6)	69 (20.4)	0.031	< 0.0001	< 0.0001
Current smoking	84 (24.6)	58 (17.0)	36 (10.6)	0.008	< 0.0001	< 0.0001
Opium abuse	52 (15.2)	26 (7.6)	22 (6.4)	0.006	0.193	0.0010

All plus-minus values are mean \pm SD; BMI: Body mass index; CV: Cardiovascular; ACS: Acute coronary syndrome; SA: Chronic stable angina; CSX: Cardiac syndrome X

Table 2. Serum biochemistry profile of the study subjects

	ACS (n = 342)	SA (n = 342)	CSX (n = 342)	P ACS vs. SA	P CSX vs. SA	P CSX vs. ACS
HDL-C (mg/dl)	41.9 \pm 10.5	42.90 \pm 9.8	44.8 \pm 10.3	0.168	0.026	0.001
LDL-C (mg/dl)	121.2 \pm 43.3	124.6 \pm 47.4	115.3 \pm 37.8	0.344	0.009	0.076
Total cholesterol (mg/dl)	206.4 \pm 51.7	207.1 \pm 53.8	194.5 \pm 44.9	0.858	0.002	0.002
Triglycerides (mg/dl)	225.0 \pm 142.8	210.6 \pm 134.5	175.7 \pm 99.6	0.174	< 0.0001	< 0.0001
FPG (mg/dl)	134.9 \pm 64.7	128.9 \pm 62.5	106.9 \pm 34.0	0.219	< 0.0001	< 0.0001

All plus-minus values are mean \pm SD; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; FPG: Fasting plasma glucose; ACS: Acute coronary syndrome; SA: Chronic stable angina; CSX: Cardiac syndrome X

Discussion

To our knowledge, our study is the largest study of CSX patients compared to patients with obstructive CAD regarding the clinical and laboratory characteristics.

Our data demonstrated that in CSX group, female to male ratio was 3:2 while some studies reported 2-3:1 ratio and suggested that CSX was a women's disease but our results showed that this claim might not be acceptable.¹⁹

According to the results of this study, all the conventional cardiovascular risk factors were significantly lower in CSX patients than ACS and SA patients. It has been shown in various studies that approximately 10-30% of patients undergoing diagnostic coronary angiography to evaluate angina-like chest pain have normal coronary angiograms.²⁰ There are approximately 1,700,000 cardiac catheterizations performed annually in the United States, resulting in 170,000 to 500,000 patients with no clear diagnosis for their chest pain after coronary angiography.^{8,20,21} Considering the invasive nature of the cardiac catheterization in addition to its high costs for healthcare systems warrants more efficient selection criteria to reduce the rate of unnecessary normal coronary angiographies and its undesirable complications and costs. The significantly different risk factor profile of CSX patients in comparison to obstructive CAD patients might enable us to develop risk scoring systems in order to more comprehensive enrollment of patients with typical angina and positive exercise test for coronary angiography.

There is consistent evidence that opium abuse is significantly higher in CAD patients (10-22%) than general population (2-2.8%) in Iranian population.^{22,23} Moreover, we recently reported that opium abuse is independently associated with the existence, severity and extension of coronary atherosclerosis in diabetic patients with chronic stable angina.⁹ In this study, we observed that the frequency of opium abuse among CSX patients was comparable to that in chronic SA patients and seems to be twofold higher than reported prevalence of opium abuse in general population (3%). On the other hand, abnormal pain perception, at least in part, has been suggested for potential pathophysiology of CSX.⁸ Several studies have concordantly shown that patients with CSX exhibit enhanced pain perception.^{17,24,25} Rosenbaum¹⁷ recently observed that patients with CSX exhibit activation of the right anterior insula cortex during angina and ST changes induced by echocardiographic dobutamine stress test, in the

absence of left ventricular wall motion abnormalities. Hyperreactivity of cardiac pain receptors, abnormal transmission and/or modulation of pain signal at subcortical level, or a variable combination of all these abnormalities, might equally account for the abnormal activation of specific pain perception areas in brain.^{8,25} As opium users have shown to have abnormal pain perception²⁶ and patients with CSX are more likely than general population to use opium, it raises this hypothesis that opium abuse might be a risk factor and even an etiologic one in a subgroup of patients with CSX; however, this warrants further evaluation in future studies.

This study had potential limitations that should be mentioned. The main limitation of this study was lack of a healthy age and sex matched group, to compare with CSX patients. Hence, the conclusions about the difference of CSX patients with healthy subjects in some instances was made indirectly through the similarity of the variable of interest in CSX and CAD groups and the consistently known difference of CAD patients with healthy subjects.

In conclusion, our study demonstrated that while CSX is more prevalent in women than men (3:2), it should not be considered as a women's disease. CSX patients have substantially lower frequency of all conventional CVD risk factors than patients with obstructive CAD. This may aid in development of novel scoring systems or enrollment criteria for angiographic evaluation of patients with typical angina and positive exercise test in order to reduce the rate of negative results.

Conflict of Interests

Authors have no conflict of interests.

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