Synergistic effect of hypertension with diabetes mellitus and gender on severity of coronary atherosclerosis: Findings from Tehran Heart Center registry

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Original Article

Abstract

BACKGROUND: We performed this study to evaluate the possible synergism between hypertension and other conventional risk factors of coronary artery disease (CAD) on an angiographic severity of coronary atherosclerosis.

METHODS: A cross-sectional study was conducted on 10502 consecutive patients who underwent coronary angiography in the cardiac catheterization laboratory of Tehran Heart Center Hospital (Tehran University of Medical Sciences, Iran), and their conventional risk factors including male gender, hypertension, diabetes mellitus (DM), dyslipidemia, smoking, and family history of premature CAD were recorded. The severity of coronary atherosclerosis evaluated by calculation of Gensini's score.

RESULTS: All aforementioned conventional risk factors of CAD were independently associated with severity of CAD. Multivariate linear regression analysis demonstrated that hypertension had synergistic effect with male gender [Excess Gensini's score: 5.93, 95% confidence interval (CI): 2.72-9.15, P < 0.001] and also with DM (Excess Gensini's score: 3.99, 95% CI: 0.30-7.69, P = 0.034) on severity of CAD. No interaction was observed between hypertension and smoking, dyslipidemia and also with a family history of CAD.

CONCLUSION: Hypertension has a synergistic effect with DM and male gender on the severity of CAD. These findings imply that more effective screening and treatment strategies should be considered for early diagnosis and tight control of hypertension in male and diabetic people for prevention of advanced CAD.

Keywords: Hypertension, Synergism, Atherosclerosis

Introduction

Cardiovascular disease (CVD) has emerged as a global epidemic and is currently the major cause of death and disability worldwide.[1-3] About 83% of CVD mortality and 86.0% of CVD disability-adjusted life years took place in low-and middle-income countries.[3] In parallel with the escalating number of developing countries undergoing the epidemiologic transition (shifting from infectious diseases to chronic diseases) and demographic transition (aging of population),[2,4] the burden of CVD will undoubtedly continue to increase in coming years. Middle Eastern countries are of special concern in this context, because in the next two decades they will face the greatest increment in the absolute burden of CVD in the world.[5,6] Hence, determining the main risk factors of CVD in these countries might have pivotal role in more comprehensive and targeted planning for prevention of CVD.

Data from the reduction of atherothrombosis for continued health registry shows that hypertension is the most common risk factor of coronary artery disease (CAD) all over the world which is present in 80.3% of patients.[7] Besides, Isfahan cohort study, Iran, demonstrated that among conventional risk factors of CAD including diabetes mellitus (DM), smoking, dyslipidemia and hypertension; the presence of hypertension imposes the highest risk for developing CAD in developing countries.[8]

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There is evidence that some of conventional risk factors of CAD have the synergistic effect on the presence of CAD.[9,10] However, possible interaction between risk factors of CAD on its severity has received little attention. Identifying such potential interactions between risk factors of CAD might lead to more timely and effective preventive interventions in special populations, who have these risk factors concurrently. With this in mind, we performed this study to evaluate the possible interaction between hypertension and other conventional risk factors of CAD on the angiographic severity of coronary atherosclerosis.

Materials and Methods

This study was a cross-sectional study derived from the Tehran Heart Center hospital's cardiac catheterization registry, Iran. Tehran Heart Center is a tertiary care cardiovascular center affiliated to Tehran University of Medical Sciences. Daily prospective data collection is performed on all patients undergoing cardiac catheterization by trained research staff, and the validity of the entered data is checked by periodical rechecking of the 5% of computerized data with hard copies. This database contains about 200 variables pertaining to the demographic data, risk factors of ischemic heart disease, glucose and lipid profile, as well as findings of non-invasive studies and also coronary catheterization.

Between March 2010 and March 2012, 19128 consecutive patients (aged between 18 and 80 years) underwent elective diagnostic coronary angiography at cardiac catheterization laboratory of our center. After excluding patients with a history of previous percutaneous coronary intervention (PCI) (n = 889) or coronary artery bypass grafting (CABG) surgery (n = 434), and those with a history of previous myocardial infarction (n = 7303), a total of 10502 patients were retained for final analyses. The study protocol was approved by the Ethics Committees of Tehran University of Medical Sciences and Tehran Heart Center (Approval date: 2009/03/03-Approval number: 88-01-30-8399). Investigators guaranteed to use the medical documents of the study participants secretly. The analysis was performed on a dataset with unique patients' codes for each record without direct visibility of patients' identity.

Qualified trained staff measured waist circumference (WC) and blood pressure prior to coronary angiography. WC was measured at the minimum circumference between the iliac crest and the rib cage at minimal respiration.[11,12] For measuring the blood pressure, the subjects remained at rest for at least 15 minutes then the same staff measured blood pressure on the right arm at the sitting position.[12,13]

The family history of premature CAD was defined as a positive history of CAD including angina, angiographically determined CAD, CABG, PCI, myocardial infarction, and/or sudden cardiac death without obvious cause diagnosed at age less than 55 years for male first-degree relatives or less than 65 years for female first-degree relatives.[14]

Current smoking was defined as a regular or occasional use of tobacco in the last year.[14]

Dyslipidemia was defined as presence of any of the following:

- Total cholesterol (TC) level > 200 mg/dl,
- Low-density lipoprotein cholesterol (LDL-C) level > 130 mg/dl,
- High-density lipoprotein cholesterol (HDL-C) level < 40 mg/dl,
- Triglyceride (TG) level > 150 mg/dl,
- Patients receiving lipid-lowering agents because of diagnosis of dyslipidemia made by a physician.[14]

Hypertension was defined by any one of the following:

- History of hypertension diagnosed and treated with medication, diet and/or exercise
- Prior documentation of blood pressure greater than 140 mmHg systolic and/or 90 mmHg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure greater than 130 mmHg systolic and/or 80 mmHg diastolic on at least two occasions for patients with diabetes or chronic kidney disease
- Currently on pharmacologic therapy for treatment of hypertension systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or currently receiving antihypertensive treatments.[14]

DM was defined as fasting blood sugar (FBS) ≥ 126 mg/dl in two measurements, or a random blood sugar level ≥ 200 mg/dl and/or use of the antiglycemic agents.[14]

All pre-procedural blood biochemistry assays for patients scheduled for coronary catheterization in our center are performed in the Tehran Heart Center Laboratory with adherence to external quality control. Peripheral venous blood specimens are collected from an antecubital vein after 10-12 hours fasting of subjects.[15] FBS is measured by the

glucose oxidation method (Pars Azmoon, Tehran, Iran) and TC, TG, and LDL-C are determined by enzyme colorimetric assay (Pars Azmoon, Tehran, Iran) using a Hitachi Autoanalyzer (type 717, Hitachi medico, Tokyo, Japan). HDL-C is measured using precipitation based method.

Coronary angiography was performed using standard techniques and recorded in multiple projections for left and right coronary arteries. In this study, all the angiograms were assessed by a cardiologist, blinded to the patients' medical and anthropometric status. Obstructive CAD was defined as ≥ 50% luminal diameter stenosis in one or more major epicardial vessel.[16]

The Gensini's score was used for the assessment of the severity of CAD. This severity score has been described previously.[17] Briefly, the coronary arterial tree was divided into segments with multiplying factors according to the geographic functional importance of any given segment (5 for the left main stem to 0.5 for the most distal segments) as well as the percent reduction in the lumen diameter. The roentgenographic appearance of concentric lesions and eccentric plaques was assigned a score (0, 1, 2, 4, 8, 16, or 32 according to the degree of luminal stenosis). The sum of the segmental scores yielded the Gensini's score.[18]

The Kolmogorov-Smirnov test was applied to examine normal distribution. Logarithmic transformation was done for non-normal distributions. The continuous variables are expressed as mean ± standard deviation (SD), and they were compared using the Student t-test. The categorical variables were compared using a chi-square test or the Fisher exact test, as appropriate, and they are presented as absolute frequencies with percentages. The predictive values of the conventional CVD risk factors for the severity of CAD were assessed via linear regression analyses. First, univariate regression analysis was employed to assess the relationship between the presence of conventional risk factors and the severity of coronary atherosclerosis and thereafter independent predictive value of each risk factor was tested using multivariate regression analysis.[11] A categorical "interaction-term analysis" was performed to assess the possible synergistic effect of hypertension with other conventional risk factors of CAD including male sex, dyslipidemia, smoking, and DM.[19] The interaction terms and also the conventional risk factors of CAD were entered into a backward stepwise multiple linear regression models to assess the independent predictors of severity of CAD. For all analysis, the SPSS software (version 13, SPSS Inc., Chicago, IL, USA) was used. All P values were 2-tailed with significance defined as P ≤ 0.050.

Results

Of a total 10502 study subjects compatible with our selection criteria (mean age of 59.2 ± 10.9 years), 5611 (53.4%) were men, and 5247 (49.9%) patients were found to have obstructive CAD. The baseline clinical and laboratory characteristics of the study patients are presented in table 1.

Table 1. Baseline clinical and laboratory characteristics of study patients[*]

Clinical characteristics	CAD		P
	Present (n = 5247)	Absent (n = 5255)	
Age (year) (mean ± SD)	62.1 ± 10.0	56.4 ± 11.1	< 0.001
Male sex [n (%)]	2308 (44.0)	2938 (56.0)	< 0.001
Waist circumference (cm) (mean ± SD)	102.1 ± 10.5	103.4 ± 11.4	< 0.001
DM [n (%)]	1888 (36.0)	1115 (21.3)	< 0.001
Systemic hypertension [n (%)]	3278 (62.6)	2638 (50.4)	< 0.001
Dyslipidemia [n (%)]	3516 (67.9)	3018 (58.1)	< 0.001
Current smoking [n (%)]	1000 (19.1)	698 (13.3)	< 0.001
Family history of CAD [n (%)]	900 (17.2)	822 (15.8)	0.048
Waist circumference (cm) (mean ± SD)	102.1 ± 10.5	103.4 ± 11.4	< 0.001
Biochemical profile			
Ln (LDL-C) (mean ± SD)	4.69 ± 0.36	4.67 ± 0.35	0.007
Ln (HDL-C) (mean ± SD)	3.70 ± 0.26	3.76 ± 0.26	< 0.001
Ln (TC) (mean ± SD)	5.17 ± 0.26	5.16 ± 0.25	0.022
Ln (TG) (mean ± SD)	5.00 ± 0.50	4.90 ± 0.49	< 0.001
Fasting glucose (mg/dl) (mean ± SD)	124.4 ± 54.1	111.2 ± 40.6	< 0.001

[*]All plus-minus values are mean ± SD.
DM: Diabetes mellitus; CAD: Coronary artery disease; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; SD: Standard deviation

Table 2. Linear regression analysis for the predictive value of conventional risk factors of coronary artery disease for severity of coronary artery disease

Characteristics	Univariate			Multivariate*		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Age (year)	0.81	0.74-0.88	< 0.001	0.79	0.72-0.87	< 0.001
Male sex	14.40	12.96-16.03	< 0.001	15.87	14.08-17.66	< 0.001
DM	14.08	12.38-15.78	< 0.001	12.98	11.18-14.79	< 0.001
Systemic hypertension	6.21	4.64-7.75	< 0.001	3.94	2.23-5.65	< 0.001
Dyslipidemia	5.90	4.29-7.51	< 0.001	5.34	3.63-7.05	< 0.001
Current smoking	7.92	5.80-10.03	< 0.001	5.10	2.87-7.33	< 0.001
Family history of CAD	1.50	−0.60-3.59	0.162	6.22	4.09-8.35	< 0.001

*Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking and family history of CAD.
DM: Diabetes mellitus; CI: Confidence interval; CAD: Coronary artery disease

Table 3. Multivariate linear regression analysis for independent predictors of severity of coronary artery disease (CAD) measured by Gensini's score

Characteristics	Coefficient	95% CI	P
Age (year)	0.80	0.72-0.87	< 0.001
Male sex	20.00	17.46-22.51	< 0.001
DM	15.66	12.63-18.69	< 0.001
Systemic hypertension	7.45	4.85-10.05	< 0.001
Dyslipidemia	4.84	3.16-6.52	< 0.001
Current smoking	5.55	3.34-7.75	< 0.001
Hypertension and male gender	5.93	2.72-9.15	< 0.001
Hypertension and DM	3.99	0.30-7.69	0.034

DM: Diabetes mellitus; CI: Confidence interval

Linear regression analysis demonstrated that all conventional risk factors of CAD including age, male sex, DM, hypertension, dyslipidemia, and positive family history of premature CAD were positively associated with severity of CAD measured as the Gensini's score even after adjustment for potential confounders (Table 2). Among conventional risk factors of CAD male gender (β = 15.87, P < 0.001) and DM (β = 15.87, P < 0.001) were the two most powerful independent predictors of the severity of CAD while systemic hypertension solely had the weakest independent association with the severity of CAD (β = 3.94, P < 0.001).

As mentioned before, we used regression-term analysis for assessment of the possible synergistic effect of hypertension with other conventional risk factors of CAD on severity of CAD. As shown in table 3 hypertension had the synergistic effect with male gender on the severity of CAD. In fact presence of hypertension in men (rather than women) results into an average 5.93 [95% confidence interval (CI): 2.72-9.15] excess Gensini's score over the expected sum of scores from both of these risk factors. Similarly, concurrent presence of hypertension and DM in a patient results into 3.99 Gensini's score (on average) over the value resulting from simply summing the adjusted scores of both of them (coefficient: 3.99, 95% CI: 0.30-7.69).

Discussion

In this study, we evaluated the independent effect of conventional risk factors of CVD on the severity of CAD. Meanwhile, we assessed the synergistic effect of hypertension with other conventional risk factors of CAD on the severity of CAD. The main findings of our study were that all conventional risk factors of CVD including age, male sex, DM, hypertension, dyslipidemia, smoking, and family history of CAD were independently associated with severity of coronary atherosclerosis. Moreover, we observed that hypertension has synergistic interaction with male gender and DM on severity of CAD which means that coexistence of hypertension with these risk factors results in excess atherosclerosis beyond that predicted by the additive effect of the individual risk factors.

Our findings are consistent with previous studies showing that clustering of multiple cardiovascular risk factors is associated with increased risk for CVD.[9,10,20] Our study demonstrated that hypertension has a more deleterious effect on coronary atherosclerosis in men than women. On the other hand, we performed an analysis in current dataset and in agreement with previous reports[8,16,21] we observed that 89.9% of our male patients were hypertensive while hypertension was found in 43.7% of female patients. These findings might be

translated into recommendation of starting the screening for hypertension at lower ages and more frequently in men than women and also to more tight control of hypertension in men.

In this study, we demonstrated a synergistic effect between hypertension and DM. In agreement with our findings, Tomiyama et al.[22] observed that raised blood pressure and raised blood glucose, even those below defining hypertension and diabetes, synergistically lead to progression of arteriosclerotic arterial damage in Japanese men. In a recent study published by Mitsutake et al.[23] it was found that gender and diabetes history were the best predictors of CAD for the patients with hypertension. The results of a recent study suggested that the coexistence of DM and hypertension augmented the production of advanced glycation end products.[24] Additional studies are proposed to clarify the underlying mechanisms of the synergistic effects of the 2 abnormalities, even in their early stage, on the accelerated progression of structural arterial stiffening.

This study has potential limitations that should be mentioned. In this study, we used Gensini's scoring system as a widespread and familiar scoring system for quantification of severity of CAD. However, at present, there are more updated and accurate scoring systems for this purpose like "Syntax score"[25] that did not administered in this study and should be acknowledged as a limitation of our study.

In conclusion, hypertension has the synergistic effect with DM and male gender on the severity of CAD. These findings imply that more effective screening and treatment strategies should be considered for early diagnosis and tight control of hypertension in male and diabetic people for prevention of CVD.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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