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The Association Between Diabetes and Coronary Artery Stenosis: A Propensity Score-Matched Case-Control Study

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ABSTRACT

Background: Background: Diabetes is a major risk factor for cardiovascular disease and is associated with increased morbidity and mortality. Controlling for confounding factors is essential when estimating its relationship with coronary artery disease. This study aimed to estimate the magnitude of the association between diabetes and coronary artery obstruction using propensity score–matched controls in a case-control study.

Methods: This case-control study was conducted on 903 patients admitted to Imam Reza Hospital in 2015, including 288 cases who underwent CABG due to coronary artery obstruction and 615 controls from non-cardiac departments. Propensity score matching was used to control for confounding variables such as age, sex, triglycerides, and blood pressure. After matching, 270 cases were matched with 270 controls. Univariate and multivariable conditional logistic regression analyses were performed on the matched data, and standard logistic regression was applied to the unmatched data. Statistical analysis was carried out using R software, version 4.0.1.

Results: Before matching, significant differences were observed between cases and controls in diabetes status, sex, age, triglycerides, and blood pressure. In the unmatched data, diabetes was strongly associated with coronary artery obstruction (OR = 4.962, 95% CI: 3.550–6.936, P < 0.0001). After propensity score matching, the odds ratio for diabetes remained significant but decreased in magnitude in the conditional logistic regression model (OR = 2.74, 95% CI: 1.888–3.9849). The marginal logistic regression model on the matched data also showed a significant association (OR = 2.51, 95% CI: 1.502–3.804).

Conclusion: Propensity score matching improved comparability between the case and control groups and provided a more accurate estimate of the association between diabetes and coronary artery obstruction. The findings indicate that diabetes remains an important risk factor for coronary artery disease, though effect estimates are smaller after adjustment for confounding.

Introduction

Coronary artery obstruction was defined as angiographically confirmed obstructive coronary artery disease, characterized by the presence of at least one significant epicardial coronary stenosis, defined as ≥70% luminal narrowing in a major non–left main coronary artery or ≥50% narrowing in the left main coronary artery (1). Coronary arteries play a vital role in supplying the heart with blood, and if they become obstructed, the individual is at risk of a heart attack. Coronary artery disease is a progressive condition that develops through the accumulation of fatty deposits on the arterial wall, leading over time to thickening of the wall and the formation of plaque layers on the arterial wall, and ultimately causing obstruction (2). Coronary artery disease is one of the leading causes of mortality worldwide (3-7).

In both developing and industrialized countries, the incidence and prevalence of heart disease are increasing rapidly (4, 8). More than three-quarters of deaths from cardiovascular disease occur in low- and middle-income countries, and Iran is part of this group. The prevalence of this disease in Iran is on the rise, to the point where it has become the leading cause of death (8, 9). Moreover, coronary artery disease is often a major cause of disability and mortality in Iran (10). Based on studies, the risk factors for cardiovascular disease and their association with coronary artery obstruction include age, diabetes, cholesterol, gender, alcohol consumption, family history, high blood pressure, obesity, smoking, and hypercholesterolemia, which together account for more than half of all deaths from cardiovascular disease (6, 8, 11-14).

Diabetes mellitus is defined as a group of metabolic disorders characterized by chronic hyperglycaemia resulting from insufficient insulin secretion, impaired insulin action, or both (15). Diabetes is one of the most common endocrine diseases, with varying prevalence across different populations (16). It is considered the most common non-communicable disease in developing countries and in the world, and currently has the fastest growth rate worldwide (17, 18). It is also the fourth leading cause of death in most developed countries. It is worth noting that heart diseases are among the major complications of diabetes and are considered the leading cause of death in these patients. In fact, 25% of deaths among patients with diabetes are due to cardiovascular diseases (19). 90% to 95% of all diabetes cases are type 2 diabetes (16). Type 2 diabetes is a complex disease that leads to continuous medical care with comprehensive strategies to reduce the risk of cardiovascular disease.

Studies have shown that the number of people with diabetes is increasing, with the incidence and mortality from cardiovascular disease in people with diabetes being 2-8 times higher than in non-diabetic individuals (20-22). Case-control studies are one of the most common study designs in analytical epidemiology and are used for such situations. The goal of such a study is to investigate potential factors that contribute to the development of a disease. In this type of study, to determine the association between an exposure (disease factor) and a specific disease, a group of individuals with the disease (cases) is considered and compared with a group of individuals who do not have the disease (controls) (23, 24).

Matching is considered one of the methods for controlling the effect of confounding variables in study design. Usually, in case-control studies, matching is used to ensure the comparability of cases and controls. In this process, the control group is selected in such a way that it is similar to the case group in terms of one or more confounding variables. Matching is usually done for two purposes: to increase the validity of the study and to control the effect of confounding variable(s) that cannot be easily controlled. When the number of confounding variables to be controlled by matching increases, we face the problem of overmatching, in which case we may not find any matched control for some patients in the case group. Also, matching using propensity scores has the ability to match patients and controls who may not be exactly the same in terms of confounding variables but are similar in terms of disease risk (25-30). The aim of this study is to estimate the magnitude of the association between diabetes and coronary artery stenosis by using propensity score–matched controls in a case-control study.

Methods

This retrospective case–control study was conducted using data from patients admitted to Imam Reza Hospital, affiliated with Mashhad University of Medical Sciences, in 2015 (1394 Iranian calendar), as recorded in the Hospital Information System (HIS). The study cohort comprised 903 participants. Of these, 288 patients with documented coronary artery obstruction or clinically significant obstructive coronary artery disease who had undergone coronary artery bypass grafting (CABG) as the revascularization procedure constituted the case group. The control group consisted of 615 hospital-based controls selected from patients admitted to the orthopedic and gastroenterology wards during the same study period, with no recorded diagnosis of coronary artery obstruction, coronary artery disease, ischemic heart disease, or history of CABG in the HIS. Patients were eligible for inclusion if information on age, sex, type 2 diabetes status, systolic blood pressure, and triglyceride level was available. Patients were excluded if they had incomplete or inconsistent records, insufficient evidence confirming coronary artery obstruction leading to CABG, duplicate records, or diabetes types other than type 2 diabetes, including type 1 diabetes, gestational diabetes, or secondary diabetes. For the control group, patients with any recorded evidence of coronary artery disease or admission to cardiovascular-related wards were also excluded.

After applying the eligibility criteria, propensity scores were estimated using age, sex, systolic blood pressure, and triglyceride level. Case–control matching was then performed using the caliper matching algorithm. The primary outcome of interest was coronary artery obstruction in diabetic patients. Potential confounding variables, including age, sex, triglyceride level (TG), and blood pressure (BP), were meticulously controlled for.

An initial univariate analysis was performed to ascertain potential confounders. Variables demonstrating a statistically significant association with both diabetes and cardiovascular disease were identified and subsequently treated as confounders. Propensity scores were calculated for all individuals in both the case and control groups using a logistic regression model incorporating the full set of identified confounders. Subsequently, propensity score matching was employed. Among the various propensity score matching algorithms, the caliper matching method was selected due to its established efficacy in minimizing bias compared to alternative approaches (31-33). This approach limited the absolute difference in propensity scores between matched case and control subjects to a predefined caliper, set at 0.2 standard deviations of the estimated propensity score. Propensity score matching was conducted using 1:1 nearest neighbor matching within this caliper. The propensity score was calculated using the following logistic regression formulation:

$$PS(y) = Pr(y = 1|\text{confounders})$$

Specifically, age, triglycerides, sex, and blood pressure were entered as covariates into the logistic regression model to estimate the propensity scores. Following propensity score matching, the data were structured into matched pairs, effectively forming blocks. Given the potential for a large number of blocks with limited sample size, standard logistic regression is prone to producing biased parameter estimates due to the estimation of nuisance parameters specific to each block. To address this, conditional logistic regression was employed, which yields unbiased estimates for the parameters of primary interest—namely, the association between risk factors and the outcome. The general formulation of the conditional logistic regression model for individually matched case–control studies is presented as:

$$logit\big(p\big((Y_{ij}=1\big|set_j)\big)\big)=\alpha_0+\beta_1X_{1ij}+\beta_2X_{2ij}+\cdots..+\beta_kX_{kij}$$

In this equation, α_j denotes the parameter specific to the j-th matched set.

To identify key factors associated with coronary artery obstruction, univariate logistic regression analyses were conducted sequentially. A significance threshold of α=0.10 was adopted during this phase to ensure the inclusion of all potentially relevant variables. Subsequently, variables achieving a univariate significance level below 0.10 were entered concurrently into a multivariable logistic regression model to assess their simultaneous effects and control for confounding. Confounding variables were systematically removed as appropriate to obtain adjusted estimates of statistically significant associations. For the propensity score–matched data, both univariate and multivariable conditional logistic regression analyses were performed. In parallel, for the unmatched data, standard univariate and multivariable logistic regression models were utilized to estimate marginal effects. The functional specifications for the conditional and marginal logistic regression models are as follows:

Conditional Logistic Regression Model:

$$logit\big(p\big((Y_{ij}=1\big|set_j)\big)\big)=\alpha_0+\beta_1X_{1ij}+\beta_2X_{2ij}+\cdots..+\beta_kX_{kij}$$

Marginal Logistic Regression Model:

$$logit(p(Y_i=1))=\beta_0+\beta_1X_{1i}+\beta_2X_{2i}+\cdots..+\beta_kX_{ki}$$

Y_i represents the outcome (coronary artery obstruction) for the i-th individual, and X_1, X_2, …, X_k denote the explanatory variables. The marginal model can be expressed as:

$$logit[P(Y_i=1)]=\alpha+\beta X_i$$

The parameter β quantifies the effect of the covariate X_i on the log-odds of the outcome. The exponentiated term, $\exp(\widehat{\beta_{ma}})$ represents the odds ratio associated with a one-unit increase in X_i. The conditional (subject-specific) model is specified as:

$$logit[P(Y_{it}=1)]=\alpha_i+\beta X_i$$

Finally, crude and adjusted odds ratios (ORs), along with their corresponding 95% confidence intervals (CIs), were estimated for each model. A comparative analysis of these estimates was subsequently performed. All statistical analyses were executed utilizing R software, version 4.0.1.

Results

This study included 903 participants. Of these, 288 individuals were assigned to the case group, defined as patients undergoing coronary artery bypass grafting (CABG) due to coronary vascular obstruction, and 615 individuals were assigned to the control group, consisting of hospital-based controls recruited from non-cardiac departments.

Table 1 presents the frequencies and mean values (where applicable) of the investigated demographic and clinical variables for all 903 participants, stratified by group and compared before and after propensity score matching. Prior to matching, the overall cohort comprised 646 females (51.4%) and 439 males (48.6%). Among the 323 participants with diabetes, 152 individuals (24.7%) were in the control group and 171 individuals (59.4%) were in the case group. The mean age in the control group was 54.49 ± 11.28 years, whereas in the case group it was 58.34 ± 9.44 years. Before matching, statistically significant differences between the case and control groups were observed for diabetes status (P<0.0001), sex (P<0.0001), age (P<0.0001), triglycerides (TG) (P=0.004), and blood pressure (BP) (P<0.0001). After propensity score matching (caliper width = 0.049), 270 cases were matched with 270 controls. Post-matching, a significant difference in diabetes status persisted between the groups (P<0.0001). While no significant difference in sex was observed after matching (P=0.922), the mean age remained comparable between groups (P=0.935). Significant differences were also noted for TG (t = value, P=0.042P = 0.042P=0.042) and BP (t = value, P=0.308P = 0.308P=0.308) after matching.

Table 2 displays the results of the univariate logistic regression analysis (baseline model) to identify factors associated with coronary artery obstruction. In this unadjusted model, diabetes was significantly associated with an increased odds of coronary artery obstruction (OR = 4.962, 95% CI: 3.550–6.936, P < 0.0001). Other variables, including sex (OR = 5.129, 95% CI: 3.627–7.253, P < 0.0001), age (OR = 1.032, 95% CI: 1.016–1.048, P < 0.0001), and TG (OR = 0.390, 95% CI: 0.188–0.809, P = 0.004), also showed significant associations. Blood pressure (BP) approached significance (OR = 0.872, 95% CI: 0.804–0.945, P = 0.0001).

Table 3 presents a comparison of odds ratios (ORs) for diabetes and their corresponding confidence intervals (CIs) across different logistic regression models. The crude OR (without matching) was 4.452 (95% CI: 3.304–4.452). The unadjusted OR from the logistic regression model (similar to crude) was 4.962 (95% CI: 3.550–6.936). After propensity score matching and fitting a conditional logistic regression model, the OR for diabetes in the case group compared to the control group was 2.74 (95% CI: ‘1.888–3.9849). The marginal logistic regression model on the matched data yielded an OR of 2.51 (95% CI: 1.502–3.804). Also, it provides estimated coefficients (β̂), standard errors (S.E.), standard errors (S.E.), bias, $Bias_2$, and mean squared error (MSE) for these models.

Table 1. Frequencies and means of study population variables before and after propensity score matching

		before matching			after matching		
		group		Chi-Square Tests p-value	group		Chi-Square Tests p-value
		control	case		control	case	
Diabetes	No	463(75.3%)	117(40.6%)		170(63.0%)	109(40.4%)	<0.0001
	Yes	152(24.7%)	171(59.4%)	<0.0001	100(37.0%)	161(59.6%)	
Sex	0	247(40.2%)	217(75.3%)	<0.0001	198(73.3%)	199(73.7%)	0.922
	1	368(59.8%)	71(24.7%)		72(26.7%)	71(26.3%)	
		Mean	**Std. Deviation**	**t-test for Equality of Means p-value**	**Mean**	**Std. Deviation**	**t-test for Equality of Means p-value**
Age	control	54.49	11.288	<0.0001	55.98	12.297	0.935*
	case	58.34	9.438		57.75	9.291	
tg1	control	2.1058	.19444	0.004	2.0846	.20458	0.042*
	case	2.0563	.26126		2.0645	.26439	
bp	control	13.08	2.388	<0.0001	12.58	2.272	0.308*
	case	12.50	1.629		12.56	1.607	

Table 2. Factors associated with coronary artery obstruction using the standard logistic regression model (baseline model).

	Variables	OR	95%CI for OR	
model	gender	5.129	3.627	7.253
	age	1.032	1.016	1.048
	bp	.872	.804	.945
	tg	.390	.188	.809
	diabetes	4.962	3.550	6.936

Table3: Comparison of odds ratios (ORs) for diabetes in the case group versus the control group based on different models

	OR	$\hat{\beta}$	S.E	bias	Bias2	MSE
Logistic model before matching	4.96(3.55, 6.94)	1.6	0.167	0.75	0.5625	0.59
Marginal logistic model on matched data	2.51(1.5, 3.8)	0.92	0.232	0.07	0.0049	0.054
Conditional logistic model on matched data	2.74 (1.89, 3.98)	1.01	0.186	0.16	0.027	0.0617
No model before matching	4.452 (3.304, 4.452)		[redacted]			
True Pure	2.34	0.85				

Discussion

Given the significance of coronary artery disease (CAD) in individuals with diabetes, its investigation is of paramount importance. In this regard, the selection of an appropriate research methodology, followed by a suitable statistical analysis capable of predicting the odds of disease development from observed data, plays a key and strategic role. The objective of this study was to examine the association between diabetes and coronary artery disease using propensity score-based matching. Employing propensity score matching and fitting the model to individuals in the two matched groups enhances accuracy and controls for the effects of confounding variables.

The results of this study demonstrated that the odds ratio (OR) for diabetes estimated in the case and control groups using a standard logistic regression model on the pre-matching data was higher than the OR for diabetes estimated in the case and control groups based on the conditional logistic regression model of the matched data. The estimation of the odds ratio is more accurate in the conditional logistic regression model applied to matched data compared to the standard logistic regression model on unmatched data. This is because, in a matched case-control study, the distribution of the confounding variables on which matching was based is similar between the two groups, and the number of cases and controls is approximately equivalent in all strata. This leads to a reduction in the variance of the parameter under investigation, an increase in statistical efficiency, and consequently, an improvement in the study's accuracy compared to the pre-matching analysis (34).

The results after matching demonstrated that the mean differences between the two groups on propensity scores were successfully equalized. Furthermore, the matching variables were not significant in the conditional and standard regression models on the matched data, indicating successful matching between the two groups with no differences in confounders. This finding is consistent with the study conducted by Song and colleagues in 2016 (35). The odds ratio obtained from the conditional logistic regression model on the matched data is 2.74. This finding is not consistent with the results reported by Aviv and colleagues, who found the prevalence and mortality of cardiovascular disease in individuals with diabetes to be 2 to 8 times higher than in non-diabetic individuals (22). The coefficients associated with CAD risk factors such as diabetes and hypertension were consistent with the findings of other studies. (36, 37). In 2017, Chan Tang Fang and colleagues conducted a retrospective study of 1397 patients, divided into two groups: those with CAD (caa) and those without, matched by age, sex, and index year. They investigated the risk factors for CAD using matched logistic regression. Their findings indicated that the adjusted odds ratios for hypertension and diabetes were 2.09 and 1.51, respectively (38).

In 2007, Marie-Hélène Bouchard and colleagues conducted a case-control study of 20,543 patients to investigate non-fatal CAD. Each case was matched with 20 randomly selected controls. The rate ratio (RR) for non-fatal CAD was determined through conditional logistic regression, adjusted for age, sex, economic status, diabetes, and hypertension. In the multivariable conditional logistic regression model, male sex (RR 1.37; 1.16, 1.63), hypertension (RR 3.54; 2.62, 4.77), and diabetes mellitus (RR 1.97; 1.20, 3.24) were identified as risk factors for CAD. (39).

In 2010, Sylvie Prévost and colleagues conducted a case-control study involving 26,783 patients and estimated the adjusted relative risk of CAD using conditional logistic regression. Their findings indicated that the risk factors for CAD were male sex, diabetes, and the development of cardiovascular disease during follow-up (31). In this study, the coefficient associated with diabetes was in the same direction as previously reported coefficients, but smaller in magnitude. In fact, previous reports have stated that the risk of CAD in diabetic patients is two to four times higher, which is consistent with the present study. (36, 37, 40).

In a case-control study conducted in 2019 involving 265 patients with acute inferior myocardial infarction and 530 age- and sex-matched control subjects, conditional logistic regression analysis identified diabetes mellitus as a significant risk factor for acute myocardial infarction (OR: 2.257; 95% CI: 1.528–3.333; $P < 0.001$) (41). In the review of other conducted studies, increased cholesterol and LDL, along with decreased HDL, have been recognized as strong risk factors for the onset of coronary artery disease (35, 36). In Penalva's study in 2008, the total cholesterol to HDL ratio was reported as the most significant factor associated with the number of coronary vessels involved (37). Similarly, in the study by Laria et al. in El Salvador, the total cholesterol to HDL ratio was reported to be significantly higher in patients with multi-vessel coronary involvement (42).

In the review of other conducted studies, increased cholesterol and LDL, along with decreased HDL, have been recognized as strong risk factors for the onset of coronary artery disease (43, 44). In Penalva's study in 2008, the total cholesterol to HDL ratio was reported as the most significant factor associated with the number of coronary vessels involved (45). Similarly, in the study by Laria et al. in El Salvador, the total cholesterol to HDL ratio was reported to be significantly higher in patients with multi-vessel coronary involvement. (46) . In the present study, comparing the groups revealed that the cholesterol to HDL ratio was significantly higher in patients with coronary artery disease. Regarding the association between blood lipid levels and the extent of coronary artery disease, Tarchalski's study found that the extent of coronary disease was related to total cholesterol, LDL, and triglycerides. (47). In the study by Natio et al., cholesterol levels and a decrease in HDL were associated with the severity of coronary artery stenosis (48).

In the study by Jin et al., serum lipid levels, including total cholesterol, LDL, and triglycerides, were also associated with the extent of coronary artery disease (41). Overall, based on the findings of the present study and other studies conducted, serum lipids—especially total cholesterol and LDL levels—reflect the extent of atherosclerotic involvement in the coronary arteries (23-25).

In the logistic regression model applied to the data before matching, the variables diabetes, age, sex, triglycerides, high-sensitivity C-reactive protein, and a history of hypertension had a significant impact on coronary artery blockage. These findings are consistent with previously conducted studies. (6, 14, 49) In the study by Rezaei Sharif et al., they aimed to predict angiographic outcomes based on measurable risk factors. Their results indicated that age, sex, high blood lipids, high blood pressure, fasting blood glucose, and hs-CRP are influential factors in coronary artery disease. Furthermore, they suggested that if blood sugar is controlled in diabetic patients, the disease would not be a risk factor for patients with coronary artery stenosis. (50)

Additionally, in this study, with the inclusion of the triglyceride variable, the effects of TC, HDL, and LDL on the incidence of coronary artery blockage were investigated. In the fitted models, none of these variables had a significant simultaneous effect on incidence. These findings contrast with the results of other studies concerning these variables. (6, 14).

Strengths and Limitations

The study addresses a clear and clinically relevant research question by examining the association between type 2 diabetes and coronary artery stenosis. In addition, the use of propensity score matching to control for several confounding variables improves the methodological rigor of the study. The potential limitation of this study is the restricted adjustment for confounding variables and the possible introduction of selection bias due to the hospital-based control group.

Conclusion

Coronary artery disease remains a major cause of disability and premature mortality worldwide. Given the high prevalence of diabetes and its potential role in cardiovascular complications, accurately estimating the association between diabetes and coronary artery obstruction is of considerable importance. In the present study, diabetes was significantly associated with increased odds of coronary artery obstruction. The difference between the estimates obtained from the standard logistic regression model and the conditional logistic regression model reflects the impact of propensity score matching in reducing imbalance between the case and control groups and improving the validity of the estimated association. However, further studies incorporating objective indicators of glycemic control, such as HbA1c, are needed to better clarify this relationship. These findings should also be interpreted in light of several limitations. Controls were selected from patients hospitalized in non-cardiac wards and may therefore not fully represent the source population of the cases, potentially introducing selection bias. In addition, the propensity score model included a limited set of variables and residual confounding from unmeasured factors cannot be excluded.

Although propensity score matching improved comparability between the groups, a small imbalance in triglyceride levels remained after matching, and standardized balance diagnostics such as SMD or Love plots were not available. Furthermore, the inverse associations observed for blood pressure and triglycerides in the adjusted model likely reflect multivariable adjustment and interrelationships among cardiometabolic risk factors rather than true protective effects.

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Ethical Approval

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethics Code: IR.MUMS.REC.1398.293).

Conflict of Interests

The authors declare that they have no known competing financial or personal interests that could have influenced the work reported in this manuscript.

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