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Risk stratification of diabetic patients with unusual cardiac symptoms using a myocardial perfusion scan

Shirin Sarejloo[1], Fatemeh Dehghani[1], Mohammad Reza Hatamnejad[2], Soodeh Jahangiri[2], Tahereh Ghaedian[1], Maryam Salimi[3], Hamed Bazrafshan Drissi[1]

Original Article

Abstract

BACKGROUND: Autonomic nervous system dysfunction in diabetic patients can result in an atypical presentation of cardiovascular disease that can be missed. We aimed to use single-photon emission computed tomography (SPECT) to assess cardiovascular disease (CAD) in diabetic patients with atypical pain to determine whether the pain above reflects the CAD.

METHOD: Diabetic patients with atypical cardiac symptoms were referred to the SPECT department. Demographic data such as age, gender, diabetes status, and other underlying diseases were gathered. A myocardial perfusion scan was then performed. The results were recorded to evaluate the risk of myocardial ischemia and the degree of coronary artery involvement in a non-invasive manner.

RESULTS: The study included 222 (177 female) subjects with mean ages of 63.01±11.62 and 59.41±9.19 in positive and negative SPECT, respectively. The most common symptoms were atypical chest pain (51.8%), followed by shortness of breath (50.5%), nausea, and syncope (0.9%). Cardiac parameters, such as the summed stress score (SSS), summed rest score (SRS), total perfusion deficit in stress (TPD-s), total perfusion deficit in rest (TPD-r), were significantly higher in the group with coronary artery involvement (P<0.001). However, ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volumes (ESV) parameters were not (P=.0.328, 0.351, and 0.443, respectively).

CONCLUSIONS: The mere presence of diabetes does not necessitate any additional diagnostic tests beyond those required for the general population, and it is possible to follow a diagnostic course similar to that of the general population.

Keywords: Diabetes Mellitus, Coronary Artery, Myocardial Perfusion Scan, Atypical Presentation, Atherosclerosis

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Introduction

Although the risk of cardiovascular events in diabetic patients has decreased substantially in recent decades, it remains higher than in the general population. Furthermore, many people with diabetes do not survive their first cardiovascular event; if they do, their mortality is higher than those without diabetes[1, 2]. The issues above have made cardiologists more sensitive to any atypical pain among people with diabetes, causing them to perform excessive and even illogical evaluations of cardiac events.

On the other hand, the clinical implications of coronary disease in diabetic patients with altered pain perception remain debatable. Some researchers have found no differences in atypical or silent coronary cardiac disease (CAD) presentations in diabetic patients compared to non-diabetics[3-5]. In contrast, others reported that the presentation above is

1- Al-Zahra Charity Hospital, Department of Cardiology Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
2- Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
3- Shiraz University of Medical Sciences, Shiraz, Iran
Address for correspondence: Hamed Bazrafshan Drissi; Department of Cardiology Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. Email: hamedbazrafshan@yahoo.com

more frequent in diabetic patients with acute myocardial infarction[6, 7], implying that some associate type 2 diabetes with cardiovascular disease[8]. The patients above are admitted to the hospital and subjected to additional testing, imaging, and even invasive procedures such as coronary angiography. This approach leads to unnecessary hospitalization and cost.

There are several methods for assessing CAD. Angiography, considered an invasive method, detects various amounts of CAD regardless of whether myocardial perfusion was compromised. On the other hand, Single-photon emission computed tomography (SPECT) can distinguish those CADs causing a defect in myocardial perfusion[9].

According to the preceding, we aimed to assess the risk of ischemia in those diabetic patients with atypical problems. We used SPECT, which is non-invasive and less expensive than diagnostic angiography.

Materials and Methods

All diabetic patients with unusual cardiac symptoms referred to the clinical centers between April 2018 to April 2019 were included in this cross-sectional study. A readily available sampling method was used for this study. Past medical history of diabetes, the presence of any of the unusual cardiac symptoms such as non-angina Pectoris (spotted, burning, or related to breathing), shortness of breath, nausea, vomiting, abdominal pain, weakness, lack of significant electrocardiogram (ECG) change, and standard cardiac-related biomarkers were all considered inclusion criteria. Diabetic patients with a positive history of myocardial infarction, valvular disorders, pulmonary artery hypertension, ejection fraction less than 55%, previous coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) were excluded from the study.

All patients included in our study provided written informed consent. The purpose of this study was fully explained to the patients, and they were assured that the researcher would keep their information confidential. Similarly, IRBs of the authors' affiliated institutions have approved this research.

Demographic data, such as age and gender, were collected along with diabetes-related information such as duration of disease, type of diabetes, the status of follow-up, type of medication used for diabetes, and the presence of other underlying diseases. Hemoglobin A1c (HbA1c) levels were retrieved and recorded from recent tests to quantify the patient's blood sugar control. Heart SPECT was performed in these patients to assess the risk of myocardial ischemia and the extent of coronary artery involvement in a non-invasive manner. The results were recorded and re-interpreted by the scanning faculty. Patients who had CAD based on SPECT results were classified as positive, and those with no evidence of CAD (negative group) were compared regarding various parameters.

The cardiac-related parameters including summed stress score (SSS), summed rest score (SRS), total perfusion deficit in stress (TPD-s), total perfusion deficit in rest (TPD-r), ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volumes (ESV) were assessed in all involved patients. Then the obtained values were compared between the two groups.

Statistical analysis

Descriptive statistics, including mean and dispersion indices, such as the amplitude of changes and standard deviation for quantitative variables and frequency percentage for qualitative variables, were used to describe the data. The data's normality was checked using the Shapiro-Wilk test and kurtosis and skewness indices. Data analysis was performed using Independent T-Test and Chi-Square Test or Fisher's Exact Test if the Chi-Square statistic was inappropriate. Likewise, the odds ratio and 95% confidence interval were calculated using the logistic regression model. Statistical Package for the Social Sciences (SPSS) statistical software version 22 was used for data analysis [10]. P-value <0.05 was considered statistically significant.

Results

A total of 222 subjects met the eligibility criteria, were enrolled, and followed up until the end of our study. Among these, 49 (22.1%) had some degree of coronary artery disease, and 173 (87.9%) were considered normal, and these two groups were used as a basis for further comparisons in subsequent analyses. Table 1 demonstrates the demographic data between the two groups and the type and duration of diabetes in each group. Table 2 demonstrate frequency of coronary artery involvement based on cardiac scans in both groups it was shown 77.9% of patients were normal.

The age difference between the two groups with and without coronary artery involvement is statistically significant, with the subject having a higher mean age. Men were also significantly more likely to have coronary artery disease (CAD) than women (95% CI-1.17 92 4.92 and OR = 2.4).

There was no significant difference between the two types, nor was there a difference in the duration of diabetes or the level of HbA1c in CAD (P-value: 0.127, 0.761, and 0.699, respectively).

Table 3 compares the types of drugs used in the two groups in any of the drugs tested.

Table 1. Demographic data of diabetic patients with positive and negative SPECT

Variable		Study Groups		P. value
		Positive SPECT [c] n= 49	Negative SPECT n= 173	
*Age: year± SD [a]		63.0± 11.6	59.4± 9.19	0.024
**Sex: number (%)	Female	33 (67.3)	144 (83.2)	0.015
	Male	16 (32.6)	29 (16.8)	
**Type of Diabetes: number (%)	Type 1	7 (25.0)	21 (75.0)	0.127
	Type 2	42 (22.0)	149 (78.0)	
*Duration of Diabetes (year):		8.38± 6.45	8.71± 6.75	0.761
*HbA1c [b] (mmol/mol)		6.69± 1.22	6.71± 1.42	0.699

[a] SD: Standard deviation; [b] HbA1c: Glycated hemoglobin; [c] SPECT: Single-photon emission computed tomography; Binary factors are represented by number (percentage); continuous variables are illustrated as mean ± SD
* t-Test; ** Chi-square test

Table 2. The frequency and extent of coronary artery involvement based on cardiac scans in both groups

Coronary artery involvement	Frequency (%)
Normal	173 (77.9)
Mild	44 (19.8)
Moderate	3 (1.4)
Severe	1 (0.5)
Myocardial infarction	1 (0.5)
Total	222 (100)

There was no statistically significant difference between the two groups with or without coronary artery involvement.

In terms of underlying diseases and risk factors, the Chi-square test and odds ratio (OR) was used to compare the two groups with and without coronary artery involvement, proven by SPECT. According to the analysis summarized in Table 3, there was no significant relationship between these factors and CAS.

In terms of signs and symptoms, the most common are chest pain (51.8%), shortness of breath (50.5%), weakness or lethargy (23.4%), nausea (0.9%), and syncope (0.9%) being the rarest (Table 4). Results of positive an negative SPECT scans among diabetic patients were shown in Table 5, except EF, EDV and ESV

Table 3. The effect of medical, family, and drug history on CAD among diabetic patients with atypical pain

variable	CAD [a] Positive n= 49	CAD [a] Negative n= 173	OR [b] (95%CI[c])	P-value
[*]Drug history				
Citalopram	0(0.0)	2 (1.1)	-	0.450
Nitrates	8 (16.8)	22 (12.7)	1.33 (0.55- 3.22)	0.514
Aspirin	11 (22.4)	56 (32.4)	0.60 (0.28- 1.27)	0.182
Statins	20 (40.8)	85 (49.1)	0.71 (0.37- 1.35)	0.303
ACEI [d]/ARB [e]	30 (61.2)	90 (52.0)	1.45 (0.76- 2.78)	0.254
Insulin	7 (14.3)	16 (9.2)	1.63 (0.63-4.23)	0.307
Oral DM [f] Medication	41 (85.4)	144 (83.2)	1.18 (0.48-2.88)	0.717
Beta-blocker	11 (22.4)	41 (23.7)	0.93 (0.43-1.98)	0.855
Diuretics	5 (10.2)	13 (7.5)	1.39 (0.47-4.13)	0.543
Pantoprazole	1 (2.0)	3(1.7)	1.18 (0.12-11.6)	0.887
Levothyroxine	0(0.0)	10 (5.8)	-	0.122
Clopidogrel	0(0.0)	2 (1.2)	-	0.450
CCBs [g]	10 (20.4)	29 (16.8)	1.27 (0.27- 2.83)	0.554
[*]Past medical history				
Asthma	0 (0.0)	1 (0.6)	-	0.919
Hypertension	38 (77.6)	113 (65.3)	1.83 (0.87-3.84)	0.105
Hyperlipidemia	26 (53.1)	93 (53.8)	0.97 (51-1.83)	0.931
Liver Disease	2 (4.1)	3 (1.7)	2.41 (0.39-14.8)	0.328
Renal Disease	2 (4.1)	6 (3.5)	1.18 (0.23-6.06)	0.839
Smoking	8 (16.8)	17 (9.8)	1.71 (0.72-4.43)	0.204
Hypothyroidism	1 (2.0)	6 (3.5)	0.58 (0.06-4.9)	0.614
Hyperthyroidism	0(0.0)	1 (0.6)	-	-
Obesity (body mass index>25)	5 (10.2)	23 (13.3)	0.74 (0.26- 2.06)	0.565
Rheumatoid arthritis	1 (2.0)	1 (0.6)	3.5 (0.22-58.4)	0.339
Cerebral vascular accident	0(0.0)	2 (1.2)	-	0.45
positive Family History	1 (2.0)	15 (8.7)	0.25 (0.02-1.7)	0.113

[a] CAD: Coronary Artery Disease; [b] OR: Odds Ratio; [c] CI: Confidence Interval; [d] ACEI: Angiotensin-Converting Enzyme Inhibitor; [e] ARB: Angiotensin Receptor Blocker; [f] DM: Diabetes Mellitus; [g] CCB: Calcium Channel Blocker
* Chi-square test; ** Fisher exact test

other variables were significant between two groups (P < 0.001).

Except for abdominal pain, there was no statistically significant difference between the two groups in terms of these symptoms (8.2% vs. 1.2%). In other words, while these symptoms do not help diagnose the disease and cannot be used as a warning sign, abdominal can predict coronary artery involvement even though it could be more accurate.

The Chi-Square test results revealed no statistically significant difference between the two groups, implying that the distribution of symptoms in both groups is the same (P-value=0.768) (Table 4).

Regarding the cardiac-related parameters, there was a statistically significant difference in SSS, SRS, TPD-s, and TPD-r. However, EF, EDV, and ESV did not show a statistically significant difference between the two groups (Table 4).

Table 4. Unusual signs and symptoms in positive and negative SPECT among diabetic patients

variable	CAD [a]		OR [b] (95%CI[c])	P-value
	Positive n= 49	Negative n= 173		
*Signs and symptoms: number (%)				
Nausea: 2	1 (2.0)	1 (0.6)	3.58 (0.22- 58.35)	0.339
Syncope: 2	2 (4.1)	0(0.0)	0(0.0)	0.450
Vertigo: 9	2 (4.1)	7(4.0)	1 (0.2- 5.02)	0.991
Abdominal pain: 6	4 (8.0)	2 (1.2)	7.6 (1.34- 42.2)	0.008
Chronic fatigue: 13	2 (4.1)	11 (6.4)	0.62 (0.13-2.92)	0.549
Dyspnea: 112	22 (44.9)	90 (62.9)	0.75 (0.39- 1.42)	0.379
Sweating: 9	1 (2.0)	8 (0.0)	0.43 (0.05- 3.52)	0.418
Weakness and lethargy: 52	14 (28.6)	38 (22.0)	1.42 (0.69- 2.91)	0.335
Atypical chest pain: 115	26 (53.1)	89 (51.4)	0.06 (0.56- 2.01)	0.842
Palpitation: 30	7 (14.3)	23 (13.3)	1.08 (0.43- 2.7)	0.858

[a] CAD: Coronary Artery Disease; [b] OR: Odds Ratio; [c] CI: Confidence Interval;
* Chi-square test or Fisher exact test

Table 5. SPECT-related results of positive and negative SPECT scans among diabetic patients

*Variable	Study Groups		P. value
	Positive SPECT [a] n= 49	Negative SPECT n= 173	
SSS [b]	7.68± 4.95	3.45± 2.87	<0.001
SRS [c]	2.54± 3.40	0.91±1.60	<0.001
TPD-s [d]	8.93± 5.71	3.99± 3.11	<0.001
TPD-r [e]	2.52±3.60	0.87± 1.46	<0.001
EF [f]	72.9± 9.46	71.2± 9.46	0.33
EDV [g]	67.6± 25.1	72.0± 25.6	0.35
ESV [h]	20.3± 12.03	22.6± 16.6	0.44

[a] SPECT: Single-photon emission computed tomography; [b] SSS: summed stress score; [c] SRS: summed rest score; [d] TPD-s: Total perfusion deficit in stress; [e] TPD-r: Total perfusion deficit in rest; [f] EF: Ejection fraction; [g] EDV: end-diastolic volume; [h] ESV: end-systolic volumes
* t-Test

Discussion

Diabetics' altered perception of cardiac-related pain is primarily attributed to autonomic neuropathy disrupting sensory heart innervation, which then influences pain thresholds[11, 12]. A subsequent study discovered that the actual prevalence of CAD among atypical diabetic patients was lower than previously thought[13, 14]. Contradictory reports, and the economic and psychological burden imposed on families and the health system for excessive workup of these patients, prompted us to evaluate the CAD in diabetic patients presenting with unusual symptoms. Diabetes, especially in young people, cannot be a sign of CAD in the presence of atypical cardiac symptoms, as will be discussed further.

In diabetic patients with favorable evidence for CAD, SSS, SRS, TPD-s, and

TPD-r were significantly higher than in negative counterparts. These findings support the utility of SPECT in detecting CAD. Previous studies in both symptomatic and asymptomatic patients have also demonstrated high SPECT accuracy[15-17]. As a result, we used it to assess the prevalence of CAD in diabetic patients exhibiting unusual symptoms.

Except for abdominal pain, there was no significant difference between atypical cardiac symptoms and CAD in diabetic patients based on our findings and statistical analysis. According to some reports, the current results favor nontypical diabetic patients[18, 19]. On the contrary, several studies have found that shortness of breath or dyspnea is a significant predictor of CAD in diabetics[20-25]. Furthermore, some researchers linked dyspnea to coronary artery disease[26]. According to the statements above, even in the absence of typical cardiac-related symptoms, dyspnea, and abdominal pain could be considered noticeable in diabetic patients for further CAD screening.

The current evidence indicates that people with diabetes with CAD were significantly older and male. However, the gender distribution in various studies is still being debated, and it appears that it cannot be an independent factor for CAD in diabetic patients[27, 28]. Older diabetic patients are more likely to have coronary artery involvement and should undergo diagnostic tests like SPECT and angiography. Zellweger et al.[28] reported a cut-off in 2014, conducting a study among 313 DM patients with abnormal myocardial perfusion single-photon emission computed tomography (MPS) and 87 DM individuals with average MPS. Paillole et al. also suggested that patients be older than 60 for more accurate screening of atypical symptomatic patients[29]. Although the sample size and the eligibility criteria were different in the studies above, all of them reported that unusual cardiac symptoms had represented CAD rarely.

In SPECT, there was no statistically significant relationship between the type of diabetes (type 1 or 2) and duration of diabetes with coronary artery disease, despite previous research suggesting that prolonged diabetics (more than 20 years after type 1 diabetes or ten years after type 2 diabetes) had a higher risk of asymptomatic ischemia and CAD[4]. Kim et al. also discovered that having diabetes for a longer duration is associated with a greater extent, prevalence, and severity of CAD[7]. Furthermore, no drugs, including various insulins and oral anti-diabetic drugs, were found to be significantly associated with coronary artery disease. However, when calculating each group's OR, it is observed that aspirin, statins, and beta-blockers have reduced the chances of CAD. This relationship may become significant as the study population grows. Aspirin's efficacy was established in a powered RCT[30] approved by Rocca et al.[31]. Gupta et al.[32] precisely described other pharmacological managements in 2019, and the beneficial use of statins, beta-blockers, and aspirin was widely discussed and approved[33].

None of the underlying diseases, positive family history, obesity, or smoking were significantly associated with coronary artery disease in the comparison between the two groups with and without coronary artery involvement. However, in other studies, the prevalence of CAD in diabetic patients taking insulin or having high blood pressure at the same time has been significantly higher[4, 29]. Some variations are due to the study population in each study. Some studies collect samples from people referred to tertiary care centers, while others collect samples from outpatient clinics. The severity of diabetes in the first group is higher than in the second group. Therefore, the results of the studies are also different. Overall, we believed that comorbidities and diabetes duration could not be considered independent risk factors for CAD.

This study had some limitations. Because the duration of diabetes was self-reported, it may have been underestimated or overestimated. Likewise, because it is a single-center study with a small sample size, it is still being determined whether the findings can be

Conclusion

To summarize what has been said thus far, the mere presence of diabetes does not necessitate more diagnostic tests than the general population, and it is possible to go through a diagnostic process similar to the general population in treating diabetic patients with unusual cardiac symptoms. This study can be a foundation for more extensive cohort studies with larger study populations and long-term follow-up of patients following the onset of unusual cardiac symptoms to assess the annual incidence of cardiovascular events and death due to cardiac causes in these patients. Similarly, diagnostic, follow-up and treatment algorithms can be developed for patients of various ages.

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