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Standard Tests Usefulness in Diagnosing Myocardial Ischemia, Alone or With Combination in Type 2 Diabetic Patients

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Abstract

Background Despite the recognition of myocardial ischemia as a unique clinical condition, there is still substantial debate on the suitable screening protocols for individuals who are at high risk for cardiac insult.

Objective To examine effectiveness of already used medical diagnostic tests in identifying myocardial ischemia in type 2 diabetic individuals.

Methods Case control research included 50 type 2 diabetic patients and a control group of 50 healthy volunteers. All participants were investigated using: exercise treadmill test (TMT), 24-hour Holter monitoring, echocardiography, electrocardiography (ECG), lipid profile, HbA1c, renal function test, and complete blood picture.

Results Myocardial ischemia was more common in males (54%), with no statistical difference in body mass index (BMI). Regarding presence of atherogenic risk factors, there was a statistically significant difference in hypertension, smoking but no statistically significant difference in hyperlipidemia. Using test combination was better than using one test alone in early diagnosis of myocardial ischemia. Concordance between TMT and Holter monitoring was the highest one in comparison to other combinations of tests.

Conclusion Diabetes mellitus itself was the major cause of ischemic heart disease rather than the other atherogenic risk factors. The combination of the three non-invasive tests in detection of myocardial ischemia give the best results, but if only two of them to be done, then it is better to select the combination with best agreement. TMT has the greatest role when combined with another test in detection of myocardial ischemia, while echocardiography has the weakest role in this regard.

Keywords Myocardial ischemia, diabetes mellitus, treadmill test, echocardiography, Holter monitoring

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List of abbreviations: ASCVD = Atherosclerotic cardiovascular disease, BMI = Body mass index, CAD = Coronary artery disease, CCTA = Coronary computed tomography angiography, ECG = Electrocardiography, IHD = Ischemic heart disease, PCI = Percutaneous coronary imaging, T2DM = Type 2 diabetes mellitus, TMT = Treadmill test

Introduction

Multiple cellular and molecular pathophysiologic factors participate in atherosclerotic cardiovascular disease (ASCVD) in type 2 diabetes mellitus (T2DM), creating the "perfect storm" for atherosclerosis. Patients with T2DM have greater atherosclerotic plaque burden, higher

atheroma volume, and smaller coronary artery lumen diameter than persons without diabetes mellitus [1].

Myocardial ischemia due to coronary atherosclerosis commonly occurs without symptoms in patients with diabetes. As a result, multi-vessel atherosclerosis often is present before ischemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of coronary artery disease (CAD) undoubtedly worsens the prognosis for survival for many diabetic patients [2].

Myocardial ischemia is an important public health issue, and its early detection may prevent many episodes of sudden cardiac death annually [2]. The presence of myocardial ischemia is a strong mortality predictor. About 70-80% of transient ischemic episodes lack anginal chest symptoms. Lack of pain in myocardial ischemia increases morbidity and mortality since patients do not seek medical treatment in a timely fashion [3].

Myocardial ischemia can lead to serious complications, including heart attack. If a coronary artery becomes completely blocked, cardiac arrhythmias due to ischemia, especially ventricular arrhythmias like ventricular tachycardia (VT) or atrial fibrillation (AF), and sudden death, due to above consequences [4].

Management for myocardial ischemia involves improving blood flow to the heart muscle. Treatment may include medications, a procedure to open blocked arteries (angioplasty) or bypass surgery [5].

Making heart-healthy lifestyle choices is important in treating and preventing myocardial ischemia [6].

Comparison between diabetic patients and nondiabetic individuals in Asymptomatic Cardiac Ischemia Pilot (ACIP) study showed that despite more extensive and diffuse coronary disease, diabetic ACIP patients tended to have less measurable ischemia during the 48-hour ambulatory electrocardiography (ECG) [7].

Although myocardial ischemia has been recognized as a distinct clinical entity, considerable controversy still surrounds the application of appropriate screening guidelines in high-risk population [8].

This study aimed to assess the treadmill test (TMT), echocardiography and Holter monitoring tests applicability and effectiveness (alone or in combination) in early detection and monitoring of myocardial ischemia in patients with T2DM.

Methods

This study was carried out from February 2022 to March 2023 at Al-Imamein Al-Kadhimein Medical City in Baghdad.

The study was designed as case control study conducted on 2 groups: Patients group, which is consisted from 50 patients with documented T2DM. In addition to control group, which is consisted of 50 healthy volunteers who are free from DM, cardiac disease and hypertension. Control group was age and sex matched with patients' group.

All of participants were instructed and informed about the aim of the study, the benefits and the risks of the tests with full explanation of tests procedures.

All patients are pre-diagnosed by an endocrinologist, or a specialist of medicine. Full history and information were taken from every patient according to a standard protocol, which include the patient's name, age, sex, body mass index (BMI), presence of atherosclerotic risk factor(s), occupation, family history, past medical history, disease duration and treatment.

Inclusion criteria

T2DM patient who has the following criteria: disease duration ≥5 years. Has one or more of additional atherosclerotic risk factors: hypertension, smoking, or hyperlipidemia. Age range: 35-65 years.

Exclusion criteria

Patients with valvular heart disease, old myocardial infarction or previous structural heart disease detected by echo should also be excluded (that is documented by echocardiography), anemia, renal failure or impairment, and any contraindication to TMT.

All the subjects in this study performed the following test:

Exercise TMT, 24 hr 3-channels Holter monitoring, echocardiography, ECG, lipid profile test, HbA1c, renal function test, complete blood picture

Method of exercise performance

Exercise TMT according to Bruce protocol was carried out for all persons participating in this study. It was done by Mortara Instrument (MPE-INC, Milwaukee, WI, USA), which is a computer connected to a treadmill and a lead cable.

Method of Holter monitoring

3-channels Holter study for 24 hr was performed to all patients and control groups by GE Holter device. Although the whole ECG was inspected for any abnormality, the interpretation was mainly for any ST depression or even ST elevation as a sign of cardiac muscle ischemia. ST depression of 1 mm or more or ST elevation of 1 mm or more was sufficient to make the Holter test positive for cardiac ischemia.

Method of echocardiography

Echocardiography was done by the same specialist in the Echocardiography Unit in Al-Imamein Al-Kadhimein, using Vivid E9 device, GE Vingmed Ultrasound AS, Norway.

Biochemical tests

HbA1c, lipid profile test, renal function tests (blood urea and serum creatinine), and complete blood picture.

Statistical methods

Data were analyzed and presented using statistical package for social sciences (SPSS) version 23 and Microsoft Office Excel 2010. Qualitative (categorical) variables were expressed as number and percentage, whereas, quantitative (numeric) variables were first evaluated for normality distribution using Kolmogorov-Smirnov test, and then accordingly normally distributed numeric variables were expressed as mean (an index of central tendency) and standard deviation (an index of dispersion).

The following statistical tests were used:

1. Chi-square test was use to evaluate association between any two categorical variables provided that less than 20% of cells have expected count of less than 5. Otherwise, Fischer exact test was used.
2. One way analysis of variance (ANOVA) was used to evaluate difference in mean of numeric variables among more than two groups provided that these numeric variables were normally distributed.
3. Independent sample t-test was used to compare means between positive group and negative group.

The level of significance was considered at P value of equal or less than 0.05.

The study was approved by the scientific and ethical committee in College of Medicine Al-Nahrain University under the registration number: EAC-17855 in 7th of December 2021.

The study complies with the with the code of ethics for human studies of the Declaration of Helsinki.

Results

Regarding demographic characteristics, there was no statistically significant difference in mean age among control and patients' groups, 54.63±7.37 years and 53.46±7.05 years, respectively (P = 0.379). The mean duration of disease in the diabetic group was 8.54±3.03 years and it ranged from 5 to 16 years. Diabetic group included showed slightly higher male

proportion than female proportion, 27 (54.0%) versus 23 (46.0%), respectively. In comparison with control group, sex proportions showed no statistical significance level (P = 0.841). There was no statistically significant difference in mean BMI among control and patients' groups, 29.08±4.03 kg/m^2, 29.35±4.28 kg/m^2, respectively (P = 0.703). The rate of hypertension was statistically significant higher in T2DM group in comparison with control group (P <0.0001). Smoking rate was higher in diabetic group (40 %), than in control group (24%) and the difference was not statistically significant (P = 0.086). There was no statistically significant difference in rate of dyslipidemia among study groups (P = 0.230) (Table 1).

Table 1. Comparison of mean age and frequency distribution according to age among study groups

Characteristic		Control group *n* = 50	Diabetes mellitus *n* = 50	*P value*
Age (years)	Mean±SD	54.63±7.37	53.46±7.05	0.379 t NS
	Range	35-64	36-65	
	35-39, *n* (%)	2 (4.0)	2 (4.0)	
	40-49, *n* (%)	13 (26.0)	10 (20.0)	0.780 C NS
	50-59, *n* (%)	20 (40.0)	25 (50.0)	
	60-65, *n* (%)	15 (30.0)	13 (26.0)	
Duration of disease (years)	Mean±SD		8.54±3.03	
	Range		5-16	
Sex	Male, *n* (%)	28 (56.0)	27 (54.0)	0.841 C
	Female, *n* (%)	22 (44.0)	23 (46.0)	NS
BMI (kg/m^2)	Mean±SD	29.08±4.03	29.35±4.28	0.703 t
	Range	17.76 -38.05	22.02 -39.56	NS
	Underweight	3 (6.0)	0 (0.0)	0.190 C
	Normal weight	5 (10.0)	7 (14.0)	NS
Hypertension	Yes, *n* (%)	0 (0.0)	28 (56.0)	<0.0001 C
Smoking	Yes, *n* (%)	12 (24.0)	20 (40.0)	0.086 C NS
Dyslipidemia	Yes, *n* (%)	22 (44.0)	28 (56.0)	0.230 C

n: number of cases; SD: standard deviation; t: unpaired t -test; C: Chi-square test; NS: Not significant; BMI: body mass index

There was statistically significant difference in TMT among study groups; positive results were greater in diabetic group (24%) than control group (6%) and the difference was statistically significant (P = 0.0012).

With respect to Holter, there was no statistically significant difference between study groups (P = 0.461) and the positive rates were as following: 6%, 10% in control group, DM group respectively. The positive rates of echocardiography showed no statistically significant difference between DM group and control group (P = 0.240).

The results of combined analysis were based on considering a positive case obtained in one or more of the following tests: TMT, Holter monitoring or echocardiography and the results were shown in table (2).

Accordingly, positive rate in control group was 18% and positive rate in diabetes mellitus group was 32%. The difference in these rates was statistically not significant (P = 0.106).

Table 2. Comparison of positive detection rates of the three investigation techniques among study groups

Characteristic		Control group *n* = 50	Diabetes mellitus *n* = 50	*P value*
TMT	Positive, *n* (%)	3 (6.0)	12 (24.0)	0.0012 C *
	Negative, *n* (%)	47 (94.0)	38 (76.0)	
Holter	Positive, *n* (%)	3 (6.0)	5 (10.0)	0.461 C NS
	Negative, *n* (%)	47 (94.0)	45 (90.0)	
Echocardiography	Positive, *n* (%)	2 (8.0)	5 (10.0)	0.240 C NS
	Negative, *n* (%)	48 (92.0)	45 (90.0)	
Combination	Positive, *n* (%)	9 (18.0)	16 (32.0)	0.106 C NS
	Negative, *n* (%)	41 (82.0)	34 (68.0)	

n: number of cases; C: Chi-square test; TMT: Treadmill test; Echocardiography: echocardiogram; *: significant at $p \leq 0.05$; NS: not significant

Concordance rate between TMT and Holter is shown in table (3). Positive cases that were shared in common between the two methods accounted for 5 (4%) and negative cases accounted for 81 (81%). Controversial results were seen in 4 (4.0%) and 11 (11%) cases, respectively. Applying Kappa agreement statistics revealed fair agreement of 0.27.

Table 3. Concordance rate between TMT and Holter

Holter	TMT			Kappa	
	Positive	Negative	Total	Interpretation	
Positive	4 (4.0%)	4 (4.0%)	8	0.27	Fair agreement
Negative	11 (11.0%)	81 (81.0%)	92		
Total	15	85	100		

Sensitivity: 26.7%; Specificity: 95.3%; Positive predictive value (PPV): 50.0%; Negative predictive value (NPV): 88.0%; Accuracy: 85.0%

Concordance rate between TMT and echocardiography is shown in table (4). Positive cases that were shared in common between the two methods accounted for 2 (2%) and negative cases accounted for 80 (80%). Controversial results were seen in 5 (5%) and 13 (13%) cases, respectively. Applying Kappa agreement statistics revealed fair agreement of 0.10.

Concordance rate between Holter and echocardiography is shown in table (5). Positive cases that were shared in common between the two methods accounted for 0 (0.0%) and negative cases accounted for 85 (85%). Controversial results were seen in 7 (7%) and 8 (8%) cases, respectively. Applying Kappa agreement statistics revealed no agreement of -0.08.

Comparison of possible risk factors between positive cases and negative cases (based on combined results of all test)

There was no statistically significant difference in mean age, mean BMI, mean HbA1c %, proportions of sex and rate of dyslipidemia (P >0.05). Smoking rate was statistically significant higher in positive cases in comparison with negative cases, 55.6% versus 19.5%, respectively (p = 0.026) (Table 6).

Table 4. Concordance rate between TMT and echocardiography

Echocardiography	TMT			Kappa	
	Positive	Negative	Total	Interpretation	
Positive	2 (2.0%)	5 (5.0%)	7	0.10	Fair
Negative	13 (13.0%)	80 (80.0%)	93		agreement
Total	15	85	100		

Sensitivity: 13.3%; Specificity: 94.1%; Positive predictive value (PPV): 28.6%; Negative predictive value (NPV): 86.0%; Accuracy: 82.0%

Table 5. Concordance rate between Holter and echocardiography

Echocardiography	Holter			Kappa	
	Positive	Negative	Total	Interpretation	
Positive	0 (0.0%)	7 (7.0%)	7	-0.08	No agreement
Negative	8 (8.0%)	85 (85.0%)	93		
Total	8	92	100		

Sensitivity: 0.0%; Specificity: 92.4%; Positive predictive value (PPV): 0.0%; Negative predictive value (NPV): 91.4%; Accuracy: 84.0%

Table 6. Comparison of possible risk factors between positive cases and negative cases (based on combined results of all test) in the control group

Characteristic		Positive *n* = 9	Negative *n* = 41	*P value*
Age (years)	Mean±SD	56.01±8.30	54.33±6.97	0.367 I NS
BMI (kg/m^2)	Mean±SD	30.54±3.09	29.09±4.24	0.321 I NS
HbA1c %	Mean±SD	5.20±0.41	5.10±0.40	0.402 I NS
Sex	Male, *n* (%)	5 (55.6 %)	23 (55.0 %)	0.976 C NS
	Female, *n* (%)	4 (44.4 %)	18 (44.9 %)	
Hypertension	Yes, *n* (%)	0 (0.0 %)	0 (0.0 %)	---
Smoking	Yes, *n* (%)	5 (55.6 %)	8 (19.5 %)	0.026 F *
Dyslipidemia	Yes, *n* (%)	5 (55.6 %)	17 (41.5 %)	0.441 C NS

BMI: Body mass index; n: Number of cases; SD: Standard deviation; I: Independent samples t-test; C: Chi-square test; F: Fischer exact test; NS: Not significant; *: Significant at P ≤0.05

Comparison of possible risk factors between positive cases and negative cases (based on combined results of all test) in the diabetes mellitus group is shown in table 7. There was no statistically significant difference in any of these characteristics (P >0.05).

Table 7. Comparison of possible risk factors between positive cases and negative cases (based on combined results of all test) in the diabetes mellitus group

Characteristic		Positive *n* = 16	Negative *n* = 34	*P value*
Age (years)	Mean±SD	54.88 ±6.66	52.79 ±7.22	0.335 I NS
Duration (years)	Mean±SD	9.06±3.00	8.29±3.05	0.408 I NS
BMI (kg/m^2)	Mean±SD	29.18 ±4.37	29.43 ±4.31	0.850 I NS
HbA1c %	Mean±SD	7.98 ±0.78	7.58 ±1.02	0.177 I NS
Sex	Male, *n* (%)	5 (31.3 %)	18 (52.9 %)	0.151 C
	Female, *n* (%)	11 (68.8%)	16 (47.1 %)	NS
Hypertension	Yes, *n* (%)	7 (43.8 %)	21 (61.8 %)	0.231 C NS
Smoking	Yes, *n* (%)	8 (50.0 %)	12 (32.4 %)	0.322 C NS
Dyslipidemia	Yes, *n* (%)	11 (68.8 %)	17 (50.0 %)	0.544 C NS

BMI: Body mass index; n: Number of cases; SD: Standard deviation; I: Independent samples t-test; C: Chi-square test; F: Fischer exact test; NS: not significant

Discussion

In midlife, the prevalence of T2DM tends to be higher in men than in women [9]. This could explain the slight increase in male proportion than female proportion in the diabetic group of this study. Moreover, it has been noted that women have less coronary plaque burden on a per-patient level than men (with lower fibrous/fibrofatty plaque volume and total plaque volume) [10]. In addition, women show significantly slower progression of coronary atherosclerosis on serial coronary computed tomography angiography (CCTA) scans [11].

Indeed, individual comparison revealed no significant difference between diabetic group and control group; the rate of hypertension as a risk factor of ischemia was significantly higher in diabetes group in comparison with control group. This result was expected as the control group involved persons who are free from hypertension, while hypertension was significantly higher in diabetic patients as diabetes usually accompany hypertension, mostly as the latter being a risk factor or a result to diabetes [12].

There was no significant difference in rate of dyslipidemia among study groups. This could be from the treatment for almost all of patients involved that resulted in decreasing the number of patients who have dyslipidemia. Diabetic patients were on statins or primary preventive measures (they had no previous ischemic heart disease (IHD) or myocardial infarction (MI)).

There was significant difference in TMT among study group; positive results were greatest in diabetic group followed by control group and the difference was significant. It is clear that why the control group has the lowest positive results in TMT with a great difference from the control group, as the persons involved in later were healthy and free from major diseases that increase the risk for IHD like hypertension and DM. While diabetic patients may have diseased coronary arteries, and sometimes three vessel disease, without proper management or intervention because of being asymptomatic.

Regarding Holter monitoring, there was no significant difference among study groups and this could be interpreted by the probable idle life that is a common share for all patients. While the forced effort that both patients and healthy persons exposed to in TMT differentiated the two groups. Another explanation for this non-significant difference in Holter monitoring results among the both groups may be from using drugs like beta blocker in diabetic patients as a hypertensive drug or as a heart rate lowering drug. This would limit the increment in heart rate during daily activities in Holter monitoring, rendering the latter test less discriminating one. These

interpretations were adapted because of frequent absence of great exertion during Holter monitoring in majority of patients involved in this study.

The positive rates of echocardiography showed no significant difference among study groups; the rate was higher in diabetes groups than control group. This could be resulted from the more established ischemic changes in the former group than the latter group.

For getting more data analysis, a combined one was adapted in this study, not only to compare between the three tests, but also to show if there is a benefit from combing more than one of these tests in detection of myocardial ischemia in diabetic patients. This revealed that the control group has the lower percentage of positive results. This could be from the already underlying cardiac ischemia in diabetic patients that increased the positive results. While the individuals involved in the control group has no major diseases that could cause myocardial ischemia leading to more positive results in one or more of the three tests.

Another analysis of data involved combing two tests in detection of myocardial ischemia. It revealed an agreement between each two tests of the three ones that were used in this study. The greatest agreement was for TMT and Holter monitoring test, while there was no agreement for the echocardiography & Holter monitoring. It is clear from this analysis that TMT has the greatest role when combined with another test in detection of myocardial ischemia in both groups involved, while echocardiography has the weakest role in this regard. Thus, the most beneficial test combination that was revealed in this study is the one that combine TMT with Holter monitoring test.

The second beneficial test combination is the one that combine TMT with echocardiography. It also revealed a fair agreement in Kappa test, but with a lesser degree than the above combination between TMT and Holter monitoring test. Comparison of possible risk factors between positive cases and negative cases (based on combined results of all test) in the diabetes mellitus group showed no significant difference in any of them.

This may indicate that the DM itself was the major cause of IHD rather than other atherogenic risk factors. This is agreed by being DM is one the strongest risk factors for cardiovascular disease and, in particular, for IHD [13,14]. Each of these risk factors are discussed below to be in agreement or not with other studies.

Regarding BMI, this result disagreed with other studies that showed that BMI was an independent predictor of myocardial ischemia [15]. The BMI insignificance could be explained also by the effect of the control group on this analysis. The persons involved in the control group also have high BMI in general, as the diabetic patients' group, rendering this risk factor with no significant difference.

Smoking was found to be related to coronary artery disease and severity and location of the damaged artery in the heart. However, there are other studies showed that there was no significant association of smoking with the number of damaged arteries and location of arterial occlusion [16].

HbA1c is a predictive factor of severe coronary stenosis and major adverse cardiovascular events in patients with T2DM. This study showed no significant difference between positive cases and negative cases. This could be attributed to close results of HbA1c of controls and diabetic patients. Moreover, it reflects good glycemic control in the diabetic group.

In conclusion, this study showed that the DM itself was the major cause of IHD rather than other atherogenic risk factors. This is agreed by being DM is one of the strongest risk factors for IHD. Also, this study that TMT is the most applicable of the three non-invasive tests in early detection of myocardial ischemia and gives the best results. However, if two tests to be done then it is better to select the combination with best agreement of TMT & Holter monitoring. Moreover, this study revealed that TMT has the greatest role in early detection of myocardial ischemia, while echocardiography has the weakest role in this regard.

Regarding the limitations and recommendations to enhance the scope of the research, it is advisable to include

supplementary tests for the purpose of comparing the three tests under investigation. These procedures may include percutaneous coronary imaging (PCI), CT angiography, and cardiac markers.

Using a Holter device with 12 channels is more advantageous than using the one with just 3 channels for detecting myocardial ischemia. This research is limited by the lack of the suggested further tests and the absence of a 12-channels Holter device.

The sample size is rather small. Therefore, it is advisable to carry out the study on a bigger sample size. The study better to be conducted in several centers.

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Author contribution

Dr. Yousif: Collecting data, writing literature of review, analysis, concluding results. Both Dr. Al Hashimi and Dr. Hamid: Concept and methodology, supervision and reviewing manuscript.

Conflict of interest

The authors declare there is no conflict of interest.

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