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Silent Myocardial Ischemia in Diabetes: A Critical Review of Risk Factors and Screening Strategies

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ABSTRACT

Silent Myocardial Ischemia is frequent amongst diabetics as result of autonomic dysfunction and loss of pain alert mechanism. Type 2 Diabetes Mellitus patients have a higher incidence of Silent myocardial ischemia, which leads to poorer long-term cardiovascular outcomes. Cardiovascular disease is the dominant source of mortality and morbidity in diabetics. There are numerous risk factors associated with Silent myocardial ischemia in diabetes that requires earlier screening in order to prevent unexpected cardiovascular mortality, as 50% to 80% of all heart attacks are silent in nature. To achieve the suggested control over glycaemia, blood pressure, and lipids, more focus is required on guidelines-directed therapy. Conclusion: We observed that type 2 diabetics were more likely than type 1 diabetics to experience Silent myocardial ischemia. The majority of instances were observed in male patients, over 50 years of age and in patients with type 2 diabetes mellitus for 5 to 10 years.

Keywords: Coronary artery disease, Dyslipidaemia, Pulmonary hypertension, Aspirin, Macrophages, Hyperglycemia

INTRODUCTION

Clandestine ischemia, commonly referred to as "Silent Ischemia," is distinguished by cardiac perfusion anomalies during a stress test in the absence of angina and ST-segment depression greater than 1 millimetre [1]. Major cardiovascular risk factors include diabetes. Compared to the general population, those with diabetes have a 3 to 4 fold increased risk of Cardiovascular Disease (CVD) [2]. CVD is the dominant source of mortality and morbidity in diabetics [3]. Diabetes can lead to autonomic neuropathy, which can weaken any pain alert system and increase the likelihood of painless myocardial infarctions in diabetics [4]. Parasympathetic and sympathetic nerves are both impacted by cardiovascular autonomic neuropathy [5]. Damage to sensory neurons results in decreased signal transmission and inadequate or no experience of nociceptive stimuli [6]. Hence, angina in reflex to myocardial ischemia may be dampened [7]. This results in a delayed diagnosis, a delayed start to treatment, and advanced stage of coronary artery disease (CAD) [8]. Periodically, its initial manifestation may be acute coronary artery events, because myocardial ischemia in diabetic patients is quiet, prior detection through screening is critical [9]. Transient myocardial ischemia episodes can be asymptomatic; however ST segment alterations in the ECG can be noticed during treadmill tests. In high-risk diabetic individuals, it has been clearly established in recent years that silent CAD is not different from symptomatic CAD in terms of prognosis and deleterious effects [10].

Epidemiology

As per the study in 2021, there were 101 million people in India with diabetes and 136 million with pre-diabetes [11].

Men are more likely than women to have a silent heart attack, but women are more likely to die from one. Additionally, elderly adults, especially those over 75, are more likely to experience silent heart attacks. Nearly 50% to 80% of all heart attacks are silent [12].

As India is the Diabetic capital in the world, to analyse the prevalence of Silent myocardial ischemia (SMI) in patients with diabetes, we referred various Indian articles from the year 2018 to the year 2022.

Comparative prevalence of SMI in patients with diabetes

Sl.NO	Study	Year	Percentage of prevalence
1.	Rawandale Nirmalkumar et al [13].	2018	20.45%
2.	K. Shaik Anwar Hussain et al [14].	2018	36.5%
3.	C.S Sharma et al [15].	2020	17.8%
4.	Moogaambiga S et al [16].	2020	18%
5.	Abhijit Arvind Patil et al [17].	2020	21%
6.	Dr. Nuvvula Siva Krishna et al [18].	2020	28%
7.	Dr. Vivek Sharma et al [19].	2021	12.80%
8.	Nagappa H Handargal et al [20].	2021	38.9%
9.	Prashant Kumar Swarnkar et al [21].	2022	15.4%

Table 1: Various studies showing the prevalence of SMI in patients with diabetes

Classification of SMI

- Type I: The least frequent type, it manifests in patients with CAD who are fully asymptomatic and lack any anginal symptoms.
- Type II: Patients with a history of prior myocardial infarction frequently experience this type.
- Type III: This is the most prevalent type and affects people who typically have vasospastic angina or unstable angina, chronic stable angina [22].

Etiology

- Diabetes mellitus (DM): has been linked to an increased incidence of SMI and is a substantial risk factor for CAD. In diabetic individuals, cardiac autonomic dysfunction which affects pain receptors, afferent neurons, or higher brain regions is a main culprit. In individuals with DM, atherogenic dyslipidaemia is closely interrelated with an elevated risk of silent myocardial infarction and silent coronary artery disease, and treating atherogenic dyslipidaemia may assist to lessen the high remnant load of CVD.
- Previous MI: In the older population, perioperative MI occurs at a comparatively high rate. Studies showed that patients who had Coronary Artery Bypass Graft (CABG) surgery experienced Silent MI incidents that were picked up by Holter monitoring.
- Sleep apnoea: MI (silent or symptomatic), transient ischemic attack, heart failure, cardiac arrhythmias, pulmonary hypertension and stroke are all associated with obstructive sleep apnoea [23].

Signs of neuronal damage

- Dizziness or fainting
- Exercise tolerance
- Low sexual drive
- Indigestion [24].

Symptoms

Usually Silent MI patients are asymptomatic, but some may experience pain, squeezing in the centre of chest instead of left side. While some may observe

- Dizziness
- Fatigue
- Rapid heart beat
- Dyspnoea
- Acid reflux, Indigestion,
- pain in left arm, jaw and neck

- Cold sweat
- Insomnia
- Malaise
- Nausea / Vomiting [25-26].

Predisposing factors / Risk factors

Traditional risk factors for Silent MI in DM [27].	Non-Traditional risk factors for Silent MI in DM [28-29].
Age, older than 45 years in male and older than 55 years in female	Tobacco use
Lower left ventricular ejection fraction	IR hyperinsulinemia
Coexistence of carotid atherosclerosis	postprandial hyperglycaemia
Smoking and alcohol consumption	Glucose variability
Prolonged duration of diabetes,	Microalbuminuria
HbA1c levels	Thrombogenic factors
High BMI	Inflammation evidenced by elevated C-reactive protein
Dyslipidaemia (hypertriglyceridemia)	Hyperhomocysteinemia and vitamin deficiencies
Hypertension	Erectile dysfunction
Family history of heart disease	Genetics and epigenetics
Pre-eclampsia	Hematologic factors

Table 2: Traditional and Non-Traditional risk factors for Silent MI in Diabetes Mellitus

Pathophysiology

- Obesity-related insulin resistance is induced by increased tumour necrosis factor-alpha in adipose tissue, which implies that metabolic changes are driven by a subclinical inflammatory process.
- Chronic inflammation is linked to increased oxidative stress (from excessive reactive oxygen species production, increased production of advanced glycation end products, activation of protein kinase C and advected glycation end product receptor, influx of hexosamine, and polyol), and aberrant macrophage response has been increased in CAD patients with diabetes.
- Endothelial dysfunction is universal indicator of vascular disease in diabetes. Abnormal vasodilation, inflammation and a pro-thrombotic state characterize this condition.
- Hyperinsulinemia and insulin resistance also aid to endothelial dysfunction by elevating oxidative stress and reducing bioavailability of nitric oxide.
- Thrombogenesis involving abnormalities in platelet aggregation and impairment in fibrinolysis also contribute to CAD in diabetes [30-31-32].

Histopathology

- Specific histological findings within the first Twenty four hour after the injury include cardiomyocyte coagulation necrosis, neutrophil infiltration, an accretion of red blood cells in the interstitial spaces, and interstitial oedema. Ischemic cardiomyocytes with an eosinophilic appearance, lost cross-striations, and missing nuclei. Following Twenty four to Forty eight hours, coagulation necrosis fully develops. After three to five days, myocyte nuclei are destroyed, and striations are seen in the infarct's centre. After five to seven days, fibroblasts and macrophages start to emerge. At one week, neutrophil count begins to decline, and lymphocytic and plasma cells begin to infiltrate the tissue to produce granulation tissue.
- Depending on the degree of necrosis, the healing process may take as little as four weeks or as long as eight weeks to conclude. Sometimes the edges of a bigger infarct heal while leaving the centre, which contains a mummified myocyte, unhealed for an extended period of time.
- If reperfusion takes place within the first four to six hours, there is a probability that the clot will be sub-endocardial without transmural expansion. Macrophages begin to arrive on days two to three, and fibroblasts begin to appear on days three to five, along with the initial signs of healing. Patients with perfused subendocardial infarcts recover more faster than those who are not. They might be able to totally recover in as little

as two to three weeks. After six hours, significant bleeding is seen in some bigger infarcts and in individuals who need longer to receive reperfusion [33-34].

Diagnostic tests for Silent MI [35].

Sl.No	Tests	Type	Specification	Merits	Demerits
1.	Resting electrocardiogram	Non invasive	The presence of ST segment elevation and abnormal Q-waves considered as a potential MI	Cost effective	False-positive ECG changes in critically ill patients
2.	Rest cardiac magnetic resonance imaging	Non invasive	Detect and estimate the risk of MI.	No exposure to radiation	Time consuming and expensive. Obese patients cannot fit into scanners used for cardiac imaging makers
3.	Stress cardiac magnetic resonance imaging	Non invasive	Encounters CAD obstruction	Good sensitivity, No exposure to radiation	Time consuming and expensive, Respiratory artefacts can degrade image
4.	Troponin level	Invasive	Predictive marker of CV events	Dominant tool for risk quantification	Low sensitivity in very early phase of MI, limited ability to detect late minor re-infarction
5.	C-reactive protein	Invasive	Detects the elevated risk of cardiac events	Acute phase reactant	Long detection time and lower sensitivity.
6.	Carotid ultrasound	Non invasive	Uses sound waves to produce pictures of carotid arteries	Non ionizing radiation	Limited use
7.	Echocardiography	Non invasive	Detects aortic stenosis and reduced ejection fraction	No exposure to radiation and inexpensive	Operator-dependent
8.	Stress echocardiography	Non invasive	Detects stress-induced ischaemia	Easy to perform and inexpensive method	Respiratory motion artefact
9.	Exercise testing (treadmill/ cycloergometer)	Non invasive	Evaluates functional capacity (detects arrhythmias)	Widely available	Low specificity and sensitivity
10.	Single-photon emission computed tomography (SPECT)	Invasive	Identifies the location of abnormal myocardial perfusion and extent of ischemia	Provides important prognostic information	Exposure to radiation, relative expensive and time consuming
11.	Coronary flow reserve and perfusion positron emission tomography	Non invasive	Detects the existence of epicardial coronary stenosis	High degree of accuracy, less time consumption	Gives false results if chemical balances within the body are not normal
12.	Coronary artery calcium score	Non invasive	Detect coronary atherosclerosis	Safe and inexpensive method. Amount of calcium correlates with total plaque	Incapable of identifying non-calcified plaque
13.	Coronary computed tomography angiography	Invasive	Detects the diffusion of atheroma	High specificity and sensitivity	Exposure to radiation
14.	Coronary angiography	Invasive	assess coronary artery stenosis	Achieves real time dynamic image	Degree of resolution is not sufficient to allow for a precise diagnosis of lesions
15.	Fractional flow reserve (FFR)	Non invasive	assess the coronary flow during coronary angiography.	No exposure to radiation	Use supercomputer to compute FFR
16.	Urine examination	Non invasive	Microalbuminuria serves as a marker of predilection for generalized CVD	Determines protein fluctuation	Time consuming
17.	Lipid profile	Invasive	Determines the risk of MI, by measuring the fat in blood	Measures the amount of certain fat molecules in blood	Pain at site of blood withdrawal

Table 3: Various diagnostic tests for Silent MI with their Merits and Demerits

Prognosis

Despite a wealth of information on the topic, there is still debate on the prognostic significance of silent ischemia. This may be because the phrase is used so loosely to refer to a broad range of results from many investigative techniques. Stress imaging techniques can detect reversible regional

wall-motion abnormalities or induced perfusion defects, and silent ischemia can manifest as stress-provoked asymptomatic electrocardiographic changes during exercise tolerance tests or as transient, primarily asymptomatic ST-segment deviation detected during continuous ambulatory electrocardiographic monitoring. The issue is made worse by the fact that silent ischemia's prognostic significance varies depending on the clinical situation [36].

Treatment

1. Drug therapy

To achieve the suggested targets for glycemia, blood pressure, and lipids, more focus is required on guidelines-directed therapy.

Sl.No	Drug therapy	Indication
1.	Aspirin	Suggested as a primary preventative method in patients at high CV risk. 75-162 mg/dl for DM patients with increased CV risk or atherosclerotic cardiovascular disease (ASCVD)
2.	Clopidogrel	Used as alternative in patients with Aspirin allergy
3.	Dual Antiplatelet therapy	Can be utilized for 1 year following acute coronary syndrome (ACS), Prolonged use can be considered for patients with High ischemic risk, poor coronary intervention and risk of bleeding to avoid adverse CV events
4.	Aspirin + Low dose Rivaroxban	Recommended for patients with low bleeding risk, Peripheral Artery Disease (PAD) and stable CAD
5.	Angiotensin Converting Enzyme Inhibitors (ACE-I) or Angiotensin receptor blockers (ARB)	First choice antihypertensive for patient with CAD or albuminuria
6.	Beta Blockers	suggested for patients with previous MI and Heart Failure with reduced Ejection Fraction (HFrEF)
7.	Thiazide Diuretics	Preferred antihypertensive therapy
8.	Statins	High intensity statin is advised for patients with various risk factors of ASCVD.
9.	Ezetimibe and Proprotein Convertase Subtilisin Kexin type 9 inhibitors (PCSK9-I)	Recommended as adjacent treatment for patients with ASCVD and LDL ≥70mg/dl.
10.	Sodium-glucose cotransporter-2 inhibitors (SGLT2-I)	Suggested for patients with ASCVD or Heart failure who don't approach glycaemic goals through Metformin.
11.	Glucagon-like peptide-1receptor agonists (GLP-1)	Recommended for patients with ASCVD, when the weight reduction is the part of the treatment.

Table 4: Drug therapy for diabetic patients with SMI

2. Psychotherapy

Silent ischemia can be triggered by mental stress, particularly in people with underlying coronary artery disease, in such cases behavioural therapy is advisable [37-38].

3. Revascularization

Medical revascularization with percutaneous coronary procedures includes treating coronary artery blockages, either with/without stenting. The likelihood of immediate consequences such acute coronary dissection is raised. Since atherosclerosis is widespread, more and longer stents are frequently required. Acute stent thrombosis after PCI occurs more frequently in diabetic compared to patients without diabetes. Diabetes is a risk element for stent restenosis. Therefore, if the patient and their family are on board, surgical revascularization is the endorsed approach, especially in individuals with Multiple Vessel Disease (MVD) that has included the proximal left anterior descending artery (prox LAD). In spite a small increase in the early postoperative side effects, such as a higher risk of infection and slower wound healing etc. Surgical revascularization is still a therapy that the guidelines suggest. In spite of difficulties, CABG is preferable, especially in MVD with or without prox LAD, since it demonstrated improved extended results and independence from recurrent operations.

Life style measures

- Preventing hypoglycaemic episodes
- Measures to lower the resistance to insulin through weight loss programs, bariatric surgery (if body mass index is greater than 35 kg/m2), increased physical activity, and a decrease in the consumption of animal proteins are pertinent because insulin resistance is a

major factor in diabetes mellitus and its cardiovascular complications [39].

Nutrition

- To lessen the risk of CVD, a diet high in vegetables, fruits, pulses, nuts, low fat meat and whole grains is advised.
- To lower the incidence of cardiovascular episodes, replacing saturated fat with dietary monounsaturated and polyunsaturated fat, complex carbohydrates, and dietary fibre (6% of total calories) can be advantageous.
- Limiting sugary beverages and refined carbohydrates (such as those that contain less than 25% whole grain by weight) can help lower the risk of CVD events.
- Transfat consumption should be eschewed, as it is linked to higher rates of morbidity and mortality [40-41-42-43].
- Nutritional supplement
- Beta-carotene, calcium, Vitamins C, D, and E and omega-3 fatty acids are examples of nonprescription or dietary supplements that are not helpful in lowering the incidence of acute CVD events [44-45-46].

Tobacco use

- Patients who smoke frequently should be encouraged to stop at every appointment. For patients who habitually smoke tobacco, behavioural therapies are advised in addition to medication, such as bupropion, varenicline, or a mix of short- and long-acting Nicotine Replacement Therapy (NRT), to maximise quitting rates [47-48].

Alcohol use

- Alcohol shouldn't be recommended to CVD patients as a cardiovascular preventative measure [49].

Postoperative and Rehabilitation Care

After a longer stay in the hospital due to myocardial infarction, patients must be adverted to cardiac rehabilitation programmes to assist them regain their ability to exercise, learn how to manage their stress, anxiety, and depression, and control modifiable risk factors. This method will aid in lowering patient morbidity and mortality. In a patient with diabetes, risk factors for CAD must be firmly controlled. The ideal strategy would be to conduct screening ECGs while they are receiving yearly follow-up care [50].

CONCLUSION

As a result of delicate neuropathy brought on by Diabetes Mellitus, CAD in patients with diabetes is frequently asymptomatic. Diabetes mellitus produces both micro vascular and macro vascular loads. SMI is a frequent phenomenon and seems to happen more frequently in diabetic patients, most likely as a result of cardiac autonomic dysfunction. The study unequivocally shows that type 2 diabetics were more likely than type1 diabetics to experience silent MI.

Age, length of diabetes, and BMI were all strongly correlated with the incidence of SMI in T2DM, as were higher HbA1c levels, dyslipidaemia (hypertriglyceridemia), and raised postprandial blood glucose levels. The majority of SMI instances were observed in male patients over the age of 50 years and in patients with diabetes mellitus for 5 to 10 years.

It is advised that managing glucose levels is essential for preventing CAD. To reduce the risk of death from CVD, it is highly advised to screen every high-risk patient with T2DM with TMT and ECG once a year.

Abbreviations

- ACE-I: Angiotensin Converting Enzyme Inhibitors
- ARB: Angiotensin receptor blockers
- ASCVD: Atherosclerotic Cardiovascular Disease
- ACS: Acute Coronary Syndrome
- BMI: Body Mass Index
- CABG: Coronary Artery Bypass Graft
- CAD: Coronary Artery Disease
- CVD: Cardiovascular disease
- ECG: Electrocardiogram
- FFR: Fractional Flow Reserve

- HFrEF: Heart Failure with reduced Ejection Fraction
- GLP-1: Glucagon-like peptide-1
- IR hyperinsulinemia: Insulin Resistance hyperinsulinemia
- MVD: Multiple Vessel Disease
- LAD: Left Anterior Descending Artery
- LDL: Low Density Lipoprotein
- NRT: Nicotine Replacement Therapy
- PAD: Peripheral Artery Disease
- PCI: Percutaneous Coronary Intervention
- PCSK9-I: Proprotein Convertase Subtilisin Kexin type 9 Inhibitors
- SGLT2-I: Sodium-Glucose Co-Transporter-2 Inhibitors
- SMI: Silent Myocardial Ischemia
- SPECT: Single-Photon Emission Computed Tomography
- T2DM: Type 2 Diabetes Mellitus
- TMT: Treadmill Test

Author's contribution

Both the authors provided equal contribution in the preparation of the manuscript.

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