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**Atypical presentation of acute and chronic coronary artery disease in diabetics**

Hadi Khafaji HAR *et al.* Atypical presentation acute coronary syndrome

Hadi AR Hadi Khafaji, Jassim M Al Suwaidi

**Hadi AR Hadi Khafaji,** Internal Medicine Department, Toronto General Hospital, Toronto University Toronto General Hospital, Toronto University, Toronto, Ontario M5G 2C4, Canada

**Jassim M Al Suwaidi,** Qatar Cardiovascular Research Center and Heart Hospital Hamad Medical Corporation, Doha, Qatar

**Author contributions:** Hadi Khafaji HAR and Al Suwaidi JM contributed to organize and writing and reveiwng this article.

**Correspondence to: Hadi AR Hadi Khafaji,FRCPGlasgow,** Internal Medicine Department, Toronto General Hospital, Toronto University Toronto General Hospital, Toronto University, 200 Elizabeth Street, 14 EN-208 Toronto, Canada. [hadi968@hotmail.com](mailto:hadi968@hotmail.com)

**Telephone:** +1-647-4700994  **Fax:** +1-416-5955826

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**Abstract**

As diabetes mellitus advances over years with cardiovascular disease being the principal cause of mortality in diabetics and as far as chest pain is the brand symptom in patients with stable and acute coronary artery disease and while pint-size knowledge is known concerning the pervasiveness of uncommon presentations in diabetics. The symptomatology of acute coronary syndrome, comprises both pain and non-pain symptoms, may be affected by traditional risk factors such as age, gender, smoking, hypertension, diabetes, and dyslipidemia. Such atypical symptoms may range from silent myocardial iscemia to wide spectrum of non chest pain symtomes. Few studies have bring to light this under investigated subject from different parts of the world, and regrettably this aspect of ischemic heart disease has under evaluated in the major clinical trial, unfortunatly the result of which are highly diverse that makes definitive conclusion about the spectrum of atypical presenation of acute and even stable chronic coronay artery disease difficult to confirm. This may have great impact on the morbidity and mortality of coronary artery disease in diabetics. In this up to date review we will try to analyze the most recent studies about the atypical presentation of ischemic heart disease in both acute and chronic forms which may give emphasis to this under investigated topic.

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**Key words**: Diabetes mellitus; Acute coronary syndrome; Acute myocardial infarction; Ischemic heart disease; Atypical presentation; Silent myocardial ischemia

**Core tip:** Atypical presenation of of ischemic heart disease in diabetic patient both in its acute and chronic form is one of the most under investigated subject ispite of extensive reseach of coronary artery disease even in major clinical trial, according to available data from many studies till the date of writing this article the impact on out come of atypical presentation are highly conteravercial making definitive conclusion difficult which may have great impact on morbidity and mortality of acute chronic coronary artey disease in diabetics.

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**INTRODUCTION**

Cardiovascular morbidities is the main trigger of death in diabetics. Globally it is predicted that 366 million patients have diabetes mellitus by 2030. As diabetes mellitus headways over years, it results in endothelial dysfunction and changes in energy metabolism that lead to atherosclerosis in medium- and large-caliber arteries, creating lesions in coronary, cerebrovascular and peripheral arteries. Additionally atherosclerotic plaque tends to develop much earlier, advance more swiftly and be more diffuse in diabetic patients when matched to non diabetics. All these factors contribute to two to four fold higher risk of cardiovascular events in diabetics compared to non-diabetics, with cardiovascular ailment being the main source of death. The combined mortality rate from cardiovascular disease and diabetes mellitus is 245/ 100000 populations for adults aged 30 to 70 years according to World Health Organization (WHO) report[1-3].

The overall frequency of coronary artery disease (CAD) towering to 55% among diabetics. Till the date of writing this article, 90% of the published studies present data on atypical presentation of chronic and acute ischemic heart disease are carried out with type 2 diabetes, there is scarcer data available for type 1 diabetes. Consequently, most of our conclusions in this review spotlight on type 2 diabetes[4-6].

Given that diabetics frequently present with silent myocardial ischemia (SMI), with the absence of an imperative clinical “warning symptom”. Statistics from the Framingham study put forward that asymptomatic patients with various risk elements have an yearly cardiac mortality rate of approximately 3%[4,5,7]. Such outcomes from the collected works put onward numerous questions regarding diabetes mellitus and CAD: Why is myocardial ischemia repeatedly atypical or silent in diabetic patients? In what way it be unearthed? What is its aftermath? How we supposed to be dealt with? The current analysis will tackle these issues. We identified studies via MEDLINE, PubMed, EMBASE, and Current Contents searches and by reviewing reference lists search of all the studies performed in the last 30 years from both developed and developing world using keyword search: diabetes mellitus, acute coronary syndrome(ACS), acute myocardial infarction (AMI), ischemic heart disease, atypical presentation, silent myocardial ischemia with an attempts to provide conclusion and future perspective on this under evaluated topic according to up to date studies from different parts of the world.

**POSSIBLE EXPLANATION OF ATYPICAL PRESENTATION OF ACUTE CORONARY SYNDROME IN DIABETICS AND THE PROGNOSTIC IMPLICATIONS**

Chest pain is the cornerstone symptom of ACS. Nevertheless, data concerning the prevalence of an atypical presentation among these patients and its relation to subsequent care is scarce. CAD has specificities in diabetics; with pervasive atherosclerosis; diabetic patients are also more frequently asymptomatic, with wide range of atypical presentation which gives challenges in the diagnosis of CAD. As well, diabetic patients with CAD have shoddier outcomes than non-diabetics. CAD is the foremost source of morbidity and mortality in diabetic patients with higher mortality after an acute cardiac event compared to non-diabetics such inconsistencies may be related to the sternness and degree of CAD in diabetics, the magnitude of left ventricular remodeling, and the occurrence of significant ventricular dysrhythmias[8-27].

In spite of the reality that CAD is the primary vascular complication of diabetes, significant gap in our knowledge and understanding exist about atypical ACS symptoms in diabetic. Conventional risk factors, such as, hypertension, diabetes, hypercholesterolemia and smoking had great impact on the symptomatology of ACS and stable angina, including both pain and non-pain symptoms. Though numerous investigation on diabetes management, few research focused on atypical ACS symptoms in patients with diabetes with rather contradicting results. diabetics may have a diminished awareness of ischemic chest pain which could result in uncharacteristic presentation. This may be explained by autonomic neuropathy and prolongation of the anginal perceptual threshold[28]. Besides that, diabetic patients with silent myocardial ischemia(SMI) have evidence of a disseminated abnormality in metaiodobenzylguanidine (MIBG) uptake and on positron emission tomography, similar finding has also been spotted in asymptomatic diabetic patients on stress testing with dipyridamole stress myocardial scan and contrast echocardiography in about 60% of diabetic patients, all such findings reflects abnormal pain perception interrelated to sympathetic denervation[29]. SMI has been seen more frequently in diabetic patients than in the general population. SMI may be the main atypical presentation that has been sought in major clinical trials compared to other forms of atypically presented CAD in both acute and chronic forms. However, the exact prevalence of SMI remains unidentified[30]. In general, the frequency of silent CAD diverges according to the test used and on the patients’ population investigated. The prevalence of silent CAD is 6%-23% in low-risk diabetics, or as high as 60% in high-risk diabetic patients. recently it has been well recognized that silent CAD has similar prognosis and adverse events rate compared to symptomatic coronary artery disease[31]. Possible explanations for the dissimilar forms of symptoms in patients with diabetes mellitus, comprising central mechanisms such as altered thresholds of pain sensitivity, Beta-endorphin levels, in addition to autonomic neuropathy resulting in sensory denervation. The American Diabetes Association states in its agreement that patients with symptomatic autonomic neuropathy are at increased risk for sudden death; nevertheless it still controversial if adequate scientific data available to accomplish that cardiac autonomic neuropathy contributes to silent ischemia and whether specific diabetic patients might gain benefit from routine testing for occult ischemia[31].

In the last several years, diabetics have not experienced the same decline in CAD -related mortality as non-diabetics. The poor prognosis associated with diabetes after AMI has been witnessed in several studies despite adjustment for age, sex, coronary risk factors[12,13,15-20] and associated comorbidities[32]. Contradictory evidance available concerning the morbidity and mortality of diabetic patients manged with insulin *vs* oral hypoglycemic agents or diet after AMI[12,18,27,32,33]. likewise uncertainity still exist in regards to the negative prognostic implications of diabetes apply equally to patients with different spectrum of ACS *i.e*., unstable angina, non–ST and ST-segment elevation AMI. It is imperative to establish whether these patients are consistently receiving proven cardiac interventions under current practices.

**SILENT MYOCARDIAL ISCHEMIA AS A MODE OF ATYPICAL PRESENTATION IN DIABETICS (TABLE 1)**

Silent myocardial infarctions/ischemia(SMI) are more frequent than formerly alleged. Up to 25% patients with CAD had suffered a silent SMI; the magnitude of the myocardium affected is in average 10% of the left ventricle muscle mass, and it is more prevelant in diabetics. The phenomenon of SMI is still debatable. Presence of cardiac autonomic dysfunction is the assumed factor that influences the frequency of SMI in diabetics[34].Hence the importance of identifying individuals with high risk for cardiovascular events, prior to symptom onset may be of significance. Diabetes mellitus affects vascular endothelium, causing endothelial dysfunction[35]. A study assessed the frequency, scope, and independent predictors of SMI in 2 large independent cohorts of consecutive patients without a history of MI referred for rest/stress myocardial perfusion single photon emission computed tomography. With 1621 patients registered in the derivation cohort and 338 patients in the validation cohort. SMI diagnosed in patients with a myocardial scar involving ≥ 5% of the left ventricle. In the derivation cohort, 23.3% had SMI. The median infarct size was 10% [interquartile range (IQR) 5%-15%] of the left ventricle. The occurrence of SMI was 28.5% in diabetics *vs* 21.5% in non-diabetics (*P* =0.004). Diabetes mellitus was an independent predictor for the presence of SMI [odds ratio (OR) 1.5; 95% confidence interval (CI), 1.1-1.9; *P* = 0.004]. In the validation cohort, the prevalence of SMI was 26.3%, with higher incidence in diabetics (35.8%) compared to non-diabetics (24%; *P* = 0.049). The median infarct size was 11.8% (IQR, 5.9%-17.6%) of the left ventricle. After logistic regression analysis; diabetes mellitus was a noteworthy prognosticator of the presence of SMI confirming the derivation cohort result[36].

A cross sectional study on 200 subjects (mean age; 46 +/- 10 years, 31 had diabetes) subjected to an exercise stress test. Positive test for silent ischemia seen in 19% of diabetics and 13% of non-diabetic which is statistically not significant (*P* = 0.397). Hypertension and obesity were found more frequently in diabetics (48% *vs* 27%) (35% *vs* 18%) respectively[37]. Blood lipid levels may predict SMI in non-insulin dependent diabetes. A study included 220 asymptomatic diabetics using laboratory tests and gated Single-photon emission computed tomography with coronary angiography as confirmatory test, when gSPECT detected ischemia. Higher level of total chelesterol seen in gSPECT- positive diabetics, low density lipoprotein (LDL), and triglycerides (*P* < 0.05). High density lipoprotein (HDL) levels were lower in this group (*P* < 0.05). HDL was the most important normalized variable. In this study men had more frequent (33.3%) than women (24.8%). HDL levels were significantly lower in these patients. The association of low HDL with high triglycerides was a strong indicator of myocardial ischemia in type 2 diabetics without clinical cardiovascular signs[38].A gated myocardial perfusion SPECT in asymptomatic diabetics with high combination of cardiovascular risk factors detects SMI in a significant proportion and this seems to be related to future coronary events. Diabetic nephropathy may imply a greater likelihood of abnormal studies[39].

A study evaluated the pervasiveness of SMI in 147 in a diabetic Afro-Caribbean population. 23.1% had SMI; those recurrently had a personal history of cardiovascular disease likened to those without. On multivariate logistic-regression analyses, the adjusted odds ratios of SMI were considerably higher in patients with a personal history of cardiovascular disease (4.36, 95%CI, 1.36-13.96; *P* = 0.01) and left ventricular hypertrophy (LVH) (2.46, 95%CI, 1.03-5.86; *P* =0.04)[40].

Dobutamine stress echocardiography may be a useful diagnostic test to uncover SMI, especially in diabetic patients at high cardiovascular risk. A study of 79 diabetics (average age = 58.8 ± 11.8 years) revealed 67.1% had positive test, with a predominance of motion abnormalities in anterior area (83%). Microalbuminuria (*P* = 0.0001), inactivity (*P* = 0.0001), dyslipidemia (*P* = 0.0002), arterial hypertension (*P* = 0.001), smoking (0.003) and male sex (*P* = 0.004) are the main cardiovascular risk factors associated with positivity[41].

In the detection of ischemia in asymptomatic diabetics (DIAD) study, the largest prospective study of 4.8 years follow up period included 1123 asymptomatic persons with type 2 diabetes who randomized to either testing with stress myocardial perfusion scan or no testing. In this study 53%-75% of participants had intermediate to high cardiovascular risk had prevalence of inducible ischemia on screening ranged 21%-24% which is nearly comparable to lower-risk contestants (19%-23%). Intermediate-/high-risk who had higher cardiac event rates were greater (only significant for the UKPDS risk engine 4.2 *vs* 1.2%, *P* = 0.002). The yearly cardiac event rate was < 1% in all risk groups, apart from high-risk UKPDS group (approximately 2% per year). Surprisingly the annual cardiac event rate for intermediate/high was low and not reformed by standard testing for inducible ischemia[42].

High LDL level and higher carotid intima-media thickness are predominantly imperative issues that can foretell if a patient of non-insulin dependent diabetics are at risk for SMI. A high carotid intima-media thickness is a substitute and dependable indicator of higher risk of CAD in non insulin depandant diabetic patients, even in those without evident CAD[43].

Another study scrutinized SMI in unselected 90 middle-aged asymptomatic NIDDM patients (48 men; mean age: 49 +/- 6 years, mean of diabetes duration of 4 ± 4.2 years (range 1-21 years)) without CAD as documented by treadmill exercise test. Four percent of patients had positive test. Diabetics with SMI were older (55 ± 3 years *vs* 49 ± 6 years, *P* = 0.04), had higher fibrinogen level (372 ± 51 *vs* 307 ± 71 mg/dL, *P* = 0.04) and had lower total exercise time and peak workload (375 ± 30 *vs* 474 ± 115 s, *P* = 0.04; 7.3 ± 0.5 *vs* 8.9 ± 1.9, *P* = 0.04, respectively). Insulin resistance is related different atherosclerosis risk factors. Exercise test outcomes show increased cardiac sympathetic activity and parasympathetic withdrawal in increased insulin resistance[44].Left atrial surface area could independently predicted SMI after adjustment for established echocardiographic and inflammatory risk factors in diabetics[45]. Age and differential pulse pressure may predictor of SMI[46].

A study estimated the commonness of SMI in 353 asymptomatic Caucasian diabetic using Treadmill Test with single-photon emission computed tomography with exercise testing or dipyridamole injection with coronary angiography as confirmation test. Patients with SMI (8.5% are diabetics: 3 IDDM and 13 NIDDM) were older and have autonomic neuropathy, hypertension, dyslipidemia and higher microalbuminuria (613 ± 211 *vs* 72 ± 245 mg/d; *P* < 0.05)[47].

SMI may occur in more than 20% of asymptomatic patients with NIDDM. Conventional and evolving cardiac risk factors were not linked with abnormal stress tests, even though cardiac autonomic dysfunction was a resilient prognosticator of ischemia. using adenosine technetium-99m sestamibi single-photon emission-computed tomography myocardial perfusion imaging in asymptomatic NIDDM patients and testing the efficiency of current American Diabetes Association screening guidelines. Atotal of 1123 patients, with no known or suspected CAD randomly assigned to either stress testing and 5-year clinical follow-up or to follow-up only. In this study 22% had SMI; the sturdiest prognosticators for abnormal tests were abnormal Valsalva, male sex, and diabetes duration but not the traditional cardiac risk factors or inflammatory and prothrombotic markers. Choosing only patients who met American Diabetes Association guidelines have failed to detect 41% of patients with SMI[48]. Erectile dysfunction may become a possible indicator to identify diabetic patients to screen for SMI particularly in patients with additional cardiovascular risk factors[49]. However diabetics may have a higher prevalence of angina pectoris during daily activity than non-diabetics[50]. Using dobutamine stress echocardiography as test to detect SMI. In this study significant CAD identified in 9% of asymptomatic diabetics. Dynamic left ventricular outflow obstruction was detected in 59% of diabetics and only 22% in the non-diabetics, such result need to be investigated in future studies[51].

The association of SMI with cardiac autonomic neuropathy has been reported in few studies (Table 1). Autonomic dysfunction seen in 85.7% of diabetics with SMI *vs* 18.7% diabetics without silent ischemia (*P* = 0.001). The Incidence of SMI were meaningfully higher in patients with autonomic neuropathy (40% *vs* 10%) *P* < 0.001. Duration of diabetes was more (13 ± 1.59 years) in patients with autonomic neuropathy and systolic blood pressure was predictive of silent ischemia in diabetics[52-54].

Few other studies[55-65] had assessed different aspects of the association of SMI and diabetes (Table 1). Patients with SMI have a higher ischemic lenience in the working forearm as matched to diabetic patients with and without neuropathy. There is a quantitative and qualitative difference in ischemic tolerance between patients with SMI and patients with diabetic neuropathy[57,58]. The role of beta endorphin in diabetic patients with SMI may be less substantial than in non-diabetics; therefore, a diabetic neuropathy that affects the autonomic pain fibers that innervate the heart may be involved in the pathogenesis of SMI in diabetics and appears to be the most probable reason for absence of pain[59,60].

**ATYPICAL PRESENTATION OF ACUTE CORONARY SYNDROME IN DIABETICS**

Many reports including the major clinical trials and the sporadic studies (Table 2 and 3) have shown that diabetes mellitus is an independent predictor of atypical presentation of ACS with controversial outcome[66]. Several studies reported that diabetic patients had less pain compared to non diabetics[67-75] while other found no difference[76-81].

***Studies that have shown diabetes mellitus is predictor of atypical presentations of acute coronary syndrome (Table 2)***

In a nation-wide survey conducted on 2133 consecutive ACS patients. Who were separated into three age subgroups: < 65 years (*n* = 974), 65-74 years (*n* = 500), and ≥ 75 years (*n* = 639). The incidence of no anginal pain/atypical symptoms on presentation increased with age for all ACS patients (14%, 21%, and 32%, in the three age subgroups, respectively; *P* < 0.0001). The occurrence of ST-elevation on admission electrocardiogram decreased with advancing age (59%, 46%, and 42%, in the three age subgroups, respectively; *P* < 0.0001), while ST-depression progressively increased (14%, 24%, and 28%, respectively; *P* < 0.0001). In multivariate analysis, variables linked with no anginal pain/atypical symptoms on presentation were: history of heart failure, age, lack of past angina, diabetes, and nonsmoking. ST-elevation was inversely allied with no anginal pain/atypical symptoms on admission (OR, 0.48; 95%CI, 0.37-0.63)[68].

The greatest study to date that presents subgroup analyses by Culic´ V *et al*[69]; located that diabetes was an independent prognosticator of “atypical” presentation of AMI in women. In this prospective, observational study of fairly a large number of symptoms in 1996 patients establish that chest pain was more often reported by male, smokers, and hypertensive, non-diabetic, and hypercholesterolemia patients. Women frequently report non-chest pain other than epigastric and right shoulder pain, along with a range of non-pain symptoms. The independent predictors of atypical AMI presentation in both men and women are; diabetes mellitus (*P* = 0.0002 and *P* = 0.002, respectively), lower creatine kinase-MB fraction level (*P* < 0.0001 and *P* = 0.0003, respectively), older age (*P* = 0.001 and *P* = 0.01, respectively), and absence of smoking in men (*P* = 0.005). The independent predictors of presence of non-pain symptoms in both men and women were higher levels of creatine kinase-MB fraction (*P* = 0.01 and *P* = 0.049, respectively) and diabetes mellitus (*P* = 0.048 and *P* = 0.005, respectively); while hypercholesterolemia (*P* = 0.01)in men is the predictor of atypical presentation[69].

Recent study in South Korea scrutinized and likened the risk factor associated with atypical presentation according to the age parameter. In this study, diabetes and hyperlipidemia considerably foresaw atypical symptom in relatively young (< 70 years) age group. Otherwise, comorbid illnesses such as stroke or chronic obstructive pulmonary disease were the positive predictors in comparatively old age (> 70 years)[70].

Statistics from a prospective clinical trial of patients with symptoms indicating ACS in 10 United States hospitals during emergency assessment compared patient demographics, clinical variables, and outcomes. Of 10783 subjects, a definitive diagnosis of an ACS long-established in 24% of which 35% had AMI and 65% unstable angina. Sixty-two over one thousand percent of ACS patients and 9.8% of AMI patients had no pain. Patients with painless ischemia were more older, and more frequently females with more cardiac and related diseases. Patients with painless AMI were less likely to be admitted to critical care units. Among patients with acute infarct, logistic regression predicting lack of pain categorized age, heart failure and diabetes as the main predictors with only age and heart failure among all with ACS. After controlling for clinical features, silent acute ischemia foretold augmented hospital mortality[72].

In National Registry of Myocardial Infarction 2 (NRMI 2): a Prospective observational study in United States, included 434877 patients with MI; 33% have no chest pain on presentation to the hospital those were 7 years older than those with chest pain (74.2 *vs* 66.9 years), more likely to be females (49.0% *vs* 38.0%), have diabetes mellitus (32.6% *vs* 25. 4%) or previous cardiac failure (26.4% *vs* 12.3%) and have delayed presentation (mean, 7.9 *vs* 5.3 hours) but less likely to be diagnosed as having SMI patients were less likely to get thrombolysis or primary angioplasty (25.3% *vs* 74.0%), aspirin (60.4% *vs* 84.5%), beta-blockers (28.0% *vs* 48.0%), or heparin (53.4% *vs* 83.2%). SMAI patients had higher in hospital mortality compared to symptomatic patients (23.3% *vs* 9.3% )[73,74].

Many sporadic studies from different parts of the world both the developed and the developing countries had assessed the atypical presentation of ACS in different communities. Such studies have shown diverse results (Table 2). A study assessed 9509 healthy adults over 5 years had an average annual incidence of 3.6/1000 persons unrecognized infarcts and 5.3/1000 persons clinical ones. patients whose electrocardiograms were initially read by cardiologists as non-infarcts but by the computer as infarcts have a high rate of unrecognized infarcts in the consequent 5 years and a markedly higher 7-year mortality rate among the unrecognized infarct group *vs* non-infarct population, but significantly lower than those who developed a clinical infarct. In this study: age, left axis deviation, left ventricular hypertrophy, cigarette smoking, systolic or diastolic blood pressure, and peripheral vascular disease are significant risk factors for unrecognized myocardial infarction on multivariate analysis. Cholesterol, diabetes, anxiety, and psychosocial problems, do not play a noteworthy part in unrecognized infarcts[75].

In the Global Registry of Acute Coronary Events(GRACE study); the largest a multinational, prospective, observational study involving 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, the United Kingdom, and the United States). Of the 20881 patients, 8.4% have no chest pain, 23.8% not initially recognized as having ACS. Those have higher hospital morbidity and mortality (13% *vs* 4.3%, respectively; *P* < 0.0001) and they were less likely to receive effective cardiac medications than did patients with typical presentation. After adjusting for potentially confounding variables, excluding diaphoresis, higher in hospital mortality rates seen in patients who presented with pre-syncope/syncope (OR, 2.0; 95% CI, 1.4 to 2.9), nausea or vomiting (OR, 1.6; 95%CI, 1.1 to 2.4), and dyspnea (OR, 1.4; 95%CI, 1.1 to 1.9), and in those with painless presentations of unstable angina (OR, 2.2; 95%CI, 1.4 to 3.5) and ST-segment elevation MI (OR, 1.7; 95%CI, 1.2 to 2.2). In patients with unstable angina and non ST elevation MI 5.7% and 12.3% have atypical symptoms respectively. Additionally atypical presentation patients have less coronary angiography and subsequent revascularization, anticoagulant, antiplatelet and B-blocker therapy. Likewise these patients were less likely to receive aspirin, B-blockers, or statins after discharge, this seemingly linked to the failure to identify the diagnosis initially . Keeping in mind the higher baseline risk of the population presenting without chest pain, those with atypical presentation frequently have in hospital complications. On the other hand, the excess mortality rate seen in GRACE study was outstanding with almost 20% in hospital mortality in silent STEMI patients. Nevertheless, the absence of chest pain anticipated a greater probability of in-hospital death in all spectrum of ACS, and, even after multivariate analysis, the excess mortality rate persisted among patients with unstable angina and STEMI[76].

***Studies that have not shown that diabetes mellitus is predictor of atypical presentations of acute coronary syndrome (Table 3)***

Numerous studies[77-81] have shown that diabetes mellitus is not predictor of atypical presentation of ischemic syndrome. A study examined the disparities between Mexican Americans and non-Hispanic whites in described symptoms of AMI. The symptoms felt by patients recognized in a community-based surveillance program surveyed to establish the differences between-groups in relation to ethnicity, gender, and diabetic status. Information concerning the symptoms of 589 patients hospitalized and identified as either having definite or possible AMI (aged of 25 and 74 years). Chest pain is the most frequent complaint (83.2%), chest pressure or discomfort (67.6%), sweating (64.2%), fatigue (62.6%), dyspnea (60.3%), and arm or jaw pain (58.2%). After adjusting for age, diabetes mellitus, and gender, and relative to non-Hispanic whites, Mexican Americans frequently reported chest pain, upper back pain, and palpitations, but less likely to report arm or jaw pain. Similarly, women predominatly pronounce fatigue, dyspnea, dizziness, upper back pain, palpitations, and cough, but less frequently reported chest pain. Substantial differences perceived in older likened to younger patients' symptoms[77].

Diabetic with AMI may present similarly to non diabetics; In a prospective, observational study on patients with typical and atypical symptoms consistent with cardiac ischemia compared 216 diabetic and non-diabetic patients with AMI, 24% were diabetic, no significant difference in age (*P* = 0.13), female gender (*P* = 0.13), and time to presentation from symptom onset (192 ± 238 *vs* 251 ± 456 minutes, *P* = 0.41) For diabetic *vs* non-diabetic with AMI. Hypertension was more common in diabetic opposed to non-diabetic patients with AMI (77% *vs* 50%, *P* = 0.001), the same applied to elevated cholesterol (48% *vs* 33%, p=0.06). No significant difference between diabetics *vs* non diabetics in terms of the frequency of chest pain (OR, 1.04; 95%CI, 0.95 to 1.14, *P* = 0.30), associated symptoms, and diagnostic ECGs (OR, 1.16; 95%CI, 0.76 to 1.79, *P* = 0.53)[78].

Data from 2 registries of AMI patients presenting in hospital (MITRA PLUS with 18786 patients; North German Registry, NGR, AMI symptoms of 1042 patients were analyzed in in diabetics and non diabetics. diabetics were significantly older and more often female than non-diabetics. No differences in the incidence of pre-infarction angina between 2 groups (Mitra Plus). In NGR, severe angina during AMI perceived in 49.8% of diabetics *vs* 46.3% of non-diabetics (*P* =NS). While 16.9% of diabetics and 15.0% of non-diabetics (*P*; NS) have SMI with no disparity in extra-thoracic pain, dizziness, nausea, sweating, palpitations, radiation of angina and localization of radiating pain in diabetics *vs* non-diabetics. Severe dyspnea occurred in 29.5% of diabetics and 19.5% of non-diabetics patients (*P* = 0.003). In this analysis; apart from a higher frequency of severe dyspnea in diabetics, no difference in the clinical symptoms of AMI patients with and without diabetes mellitus. Silent or minimally symptomatic AMI is more common in non-diabetics[79]. A study surveyed symptoms differences in patients (50 women AND 50 men) with and without diabetes during an episode of unstable angina.In this study diabetics were more frequently hypercholesterolemic (83% *vs* 60%), have past cardiac history (85% *vs* 65%), and prior angiogram (85% *vs* 67%). Diabetics have less nausea (20% *vs* 40%), less squeezing (25% *vs* 48%) and less aching (25% *vs* 45%) type of pain, with more frequent hyperventilation as the presenting symptomes (27.5% *vs* 11.7%). With no difference in other cardiac symptoms seen in two the groups[80].

**SILENT AND ATYPICALLY PRESENTED MYOCARDIAL ISCHEMIA IN DIABETICS: TO SCREEN OR NOT?**

Assumed the preeminent risk of cardiovascular events and the greater commonness of silent CAD in diabetics compared to non-diabetics, screening asymptomatic diabetic patients for CAD is an alluring concept. Nevertheless, many elements dispute against instigating a wide-ranging screening program currently . Notable is the paucity of confirmed facts signifying that a prospectively utilized screening program has positive prognostic impact in asymptomatic diabetic patients. From the above reviewed studies the incidence of atypical and SMI is highly variable. Till the date, measures should be taken for insistent management of hypertension and hyperlipidemia exclusively on the basis of diabetes status, devoid of diversity based on the presence or absence of recognizable CAD. From the above available data the studies that had used stress single-photon emission computed tomography imaging have stated that around 50% abnormal imageing and 20% high-risk images, respectively. However, the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study[42] described a considerable lower percentage of abnormal SPECT images 16% and images with a very large (≥ 10% of the left ventricle) defect of 1%. We think that it is wise for the clinician to log and investigate for silent and or atypically presenting of myocardial ischemia and this applied for stable coronary artery disease in high risk diabetic patient *i.e.*, patient with long standing diabetes with diabetic complication namly diabetic neuropathy who may frequently present atypically, we suggest using test which has high specifity and sensitivity for detection of myocardial ischemia like myocardial perfusion scan and SPET scan as shown in the above studies conclusions. Keeping in mind the massive fiscal consequences of investigating all asymptomatic diabetic patients at intermediate and high risk by clinical scoring systems. Undoubtedly more investigations are desired to attend this matter.

**CONCLUSION**

Not all diabetics have the same coronary risk and, therefore, it is important to determine which investigations to perform and for which patients. This strategy is reasonable because it allows identification of patients who require a medical or an invasive (angioplasty *vs* CABG) slant, as these interventions may improve the prognosis. Patients with more than two risk factors may need further investigations with exercise stress testing which may provide supporting diagnostic and prognostic data when maximal and negative. When sub-maximal, or non-diagnostic, a second investigation with perfusion myocardial scintigraphy may be warranted keeping in consideration that in the diabetics this test may not have the same diagnostic accuracy as in the general population, but it is of prognostic value. Ischemia involving over 20%-25% of the myocardium justifies therapeutic investigation. Stress echocardiography is comparable to the scintigraphy.

The greater incidence of SMI in diabetics seems to be mostly due to the increased frequency of ischemic heart disease in diabetics. The importance of cardiac autonomic neuropathy in silent myocardial ischemia is still debatable, but the most acceptable as reasons for SMI, as discussed in above review, nevertheless studies are sporadic. The risk factors associated with SMI and atypical ischemic syndrome are the usual traditional factors *i.e.*, age, male gender, hypercholesterolemia, hypertriglyceridemia, hypertension, smoking, a family history of cardiovascular disease, insulin therapy (for type II diabetes), proteinuria, retinopathy, peripheral occlusive arterial disease. Upcoming studies need to deliberate possible approaches to augment the patient subgroup that possibly will have advantage from screening with judiciously accomplished cost-effective analyses. There is no facts till date support the the theory of using anti-ischemic medication can change the scenery of CAD in diabetic patients.

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| --- | --- | --- | --- | --- |
| **Table 1 Studies on silent myocardial ischemia as a mode of atypical presentation in diabetics** | | | | |
| **Ref.** | **Study population/** | **Study type/ country** | **Silent ischemia**  **%** | **Conclusion** |
| Arenja *et al*[36] | 1621 pts in the derivation cohort + 338 pts in the validation cohort | Derivation cohort/ Switzerland | 23.3%- 28.5% in DM and 21.5% in non-DM | DM is an independent predictor for the presence of SMI (OR, 1.5; 95%CI, 1.1-1.9, *P* = 0.004). In the validation cohort, the prevalence SMI = 26.3% (*n* = 89), while the prevalencea in diabetics (35.8%) *vs* non-diabetics (24%; *P* = 0.049) |
| Sheikh A *et al*[37] | 200 subject 31 diabetics *vs* 169 non-diabetics | a cross sectional study/ Pakistan | 19%) diabetics *vs* (13%) non-diabetics | No significant difference in the frequency of SMI in diabetics *vs* non- diabetics |
| Peña Y *et al*[38] | 220 asymptomatic NIDD | A prospective, observational, analytical study /Havana | 29.1% | Type 2 diabetics with ischemia had ↑ levels of total cholesterol, LDL and triglycerides. HDL levels significantlyb. The association of ↓ HDL with ↑ triglycerides was a strong indicator of SMI in NIDDM patients |
| Ruano Pérez R[39] | 56 asymptomatic diabetics | retrospective study | 46.4% | Moderate-severe ischemia in 10.7%, necrosis with ischemia in 5.4% and necrosis in 7.1%, diabetic nephropathy was the only factor related to an abnormal SPECT (*P* = 0.043) |
| Blanchet Deverly A *et al*[40] | 147 NIDDM patients | cross-sectional study /France | 23.1% | Multivariate logistic-regression analyses, the adjusted OR of SMI significantly ↑ in patients with a history of cardiovascular disease (4.36, 95%CI: 1.36-13.96, *P* = 0.01) and LVH (2.46, 95%CI, 1.03-5.86, *P* = 0.04) |
| Mbaye A *et al*[41] | 79 diabetics | Prospective/France | 67.1% | Predominance of motion abnormalities in anterior territory (83%). Cardiovascular risk factors associated with positivity of test: microalbuminuria (*P* = 0.0001), inactivity (*P* = 0.0001), dyslipidemia (*P* = 0.0002), arterial hypertension (*P* = 0.001), smoking (0.003) and male sex (*P* = 0.004) |
| Bansal S *et al*[42] | 1,123 NIDDM patients | Prospective/Detection of Ischemia in Asymptomatic Diabetics( DIAD) /United States and Canada (DIAD) study | 21%–24% in intermediate high risk.  19%–23% in low risk group. | Cardiac event ratesa in intermediate/high-risk. The annual cardiac event rate ≤ 1% in all risk groups. In intermediate-/high-risk participants randomized to screening *vs* no screening, 4.8-yr cardiac event rates were similar (2.5%–4.8% *vs* 3.1%–3.7%) |
| Agarwal AK *et al*[43] | 77 NIDDM | Prospective study /India | 28.9% | The prevalence of SMI similar in males and females. Serum LDL levels > 140 mg % had a significant correlation with the prevalence of silent CAD (*P* = 0.04). The difference in CCA-IMT values found to be statistically significant between the silent CAD and non-CAD groups (*P* = 0.019) |
| Ugur-Altun B *et al*[44] | 90asymptomatic NIDDM patients | Prospective / Turkey | 4% | diabetics with SMI had ↑fibrinogen level (372 ± 51 *vs* 307 ± 71 mg/dL, *P* = 0.04) had b total exercise time and peak workload (375 ± 30 *vs* 474 ± 115 s, *P* = 0.04; 7.3 ± 0.5 *vs* 8.9 ± 1.9, *P* = 0.04, respectively) |
| Chico A *et al* [47] | 353 NIDDM asymptomatic Caucasians | Prospective/ Spain | 8.5% | SMI patients were older, had↑ prevalence of autonomic neuropathy, Microalbuminuria, hypertension, and dyslipidemia than those without |
| Wackers FJ[48] | 1,123 NIDDM patients | Prospective/United States | 20% | Predictors for abnormal tests: abnormal valsalva, male sex and diabetes duration (5.2). Traditional cardiac risk factors or inflammatory and prothrombotic markers are not predictive. Ischemic adenosine-induced ST-segment depression with normal perfusion in women |
| Falcone C *et al*[50] | 618 patients with CAD | Prospective/Italy | 58% | SMI during exercise seen in 58% of diabetics and 64% non-diabetics. Both diabetics and non-diabetics with exertional SMI have ↑ heart rate values (*P* < 0.01), SBP (*P* < 0.01), rate-pressure product (*P* < 0.001), work load (*P* < 0.01) and maximum ST depression at peak exercise (*P* < 0.05) |
| Coisne D *et al* [51] | 49 diabetics and 63 non-diabetics | Prospective/France | 9% | Significant CAD detected in 9% of asymptomatic diabetics. Dynamic left ventricular obstruction observed in 59% of the diabetic population and only 22% in the non-diabetic population |
| Sukhija R *et al*[53] | 30 diabetics /30 non diabetics | Prospective/India | 46.7% | Diabetics had ↑ heart rate and greater number ofsupraventricular and ventricular ectopics, aprevalence of multi-vessel involvementand diffuse disease compared to controls. 50% of diabetics and none of the control had autonomic dysfunction. Autonomic dysfunction was present in 85.7% t of diabetics with SMI *vs* 18.7% diabetics without SMI (*P* = 0.001) |
| May O *et al*[54] | 240 diabetics | Prospective/Denmark | 13.5% | Frequency of SMI did not differ significantly between diabetics and non-diabetics. Systolic blood pressure was predictive of SMI in diabetes |
| Tamez-Pérez HE *et al*[55] | 60 NIDDM patients | Prospective/ Spain | 17% | In a 2 yr follow up, 4 diabetics developed symptomatic angina pectoris |
| Ahluwalia G *et al*[56] | 20male diabetics | Prospective/India | 50% | On exercise testing of diabetics, SMI detected in 64% of the patients with 3 vessel disease, 50% of the patients with 2 vessel disease and 20% of the patients with one-vessel disease *vs* 18% of the patients with three-vessel disease (*P* < 0.05) and in none of the patients with two- or one-vessel disease in non- diabetics |
| Tanaka T *et al*[61] | 92 NIDDM patients | Prospective / Japan | 38% | Diabetics with + ve Treadmill were more smokers, hypertension and had ↑triglyceride level compared to treadmill negative diabetics |
| Nesto RW *et al*[62] | 30 diabetics with peripheral vascular disease | Prospective /United States | 57% | 57% had thallium abnormalities, with reversible thallium defects compatible with ischemia 47% and evidence of prior, clinically SMI in 37%. Thallium abnormalities seen more frequently in diabetic with concomitant hypertension and cigarette smoking (*P* = 0.001) |
| Koistinen MJ[63] | 136 Diabetic subjects | controlled study/ Finland | 29% | Coronary angiography of 34 diabetics; 12 had significant coronary artery narrowing; seven had unimportant atherosclerosis; 15 had patent coronary arteries |
| Theron HD *et al*[64] | 52 IDDM and 87 NIDD subjects | Prospective /South Africa | See conclusion | No statistically significant relationship between any parameter and the presence of autonomic neuropathy. Atypical infarctions not limited to subjects with autonomic neuropathy, the incidence much a than general population |
| Touze JE *et al*[65] | 50 black African diabetics | Prospective /Africa | 10% | SMI is ↓ among black African diabetics than in white diabetics. The coronary lesions are mostly limited. Proximal narrowing and one vessel disease mostly combated. |
| aIncrease/higher; bDecreased /lower. CAD: Coronary artery disease; IDDM: Insulin dependent diabetes mellitus; NIDDM: Non-insulin dependent Diabetes mellitus; MI : Myocardial infarction; HDL: High density lipoprotein; LDL: Low density lipoprotein; SMI: Silent myocardial ischemia/infarction; CCA-IMT: Common carotid artery intimal medial thickness; | | | | |

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| **Table 2 Studies that have shown that diabetes mellitus is predictor of atypical presentations of Acute coronary syndrome** | | | | |
| **Ref.** | **Study population/** | **study type/ country** | **Atypical presentation %** | **Conclusion** |
| Stern *et al*[68] | 2113 ACS patients | nationwide survey/Israel | 21.7% have no chest pain | In multivariate analysis, variables associated with no anginal pain/atypical symptoms on presentation (ina order): history of heart failure, age, no past angina, diabetes and nonsmoking.18.7% of males patient have no chest pain on presentation *vs* 29.7% of females |
| Culic´ *et al*[69] | 1996 MI patients | a prospective, observational study/ Croatia | 14.8% have no chest pain | The independent predictors of atypical presentation in both gender; alevels of CK-MB fraction (*P* < 0.0001 and *P* = 0.0003, respectively), NIDDM (*P* = 0.0002 and *P* = 0.002, respectively), older age (*P* = 0.001 and *P* = 0.01, respectively), no smoking in men (*P* = 0.005)  The independent predictors of presence of non-pain symptoms; DM (*P* = 0.048 and *P* = 0.005, respectively), alevels of CK-MB (*P* = 0.01 and *P* = 0.049, respectively) and hypercholesterolemia in men (P =0.01) in both menand women |
| Hwang *et al*[70] | 931) newly diagnosed as ACS | Retrospective/ South Korea | 7.8% of younger pts and 13.4% of older pts. | A logistic regression analysis after adjustment for the gender and ACS type, indicate; diabetesand hyperlipidemia significantly predicted atypical symptoms in the younger patients |
| MacKenzie *et al*[71] | 64 (12 women with DM) | Descriptive,  cross-sectional / Canada | See conclusion | Less chest pain in diabetics *vs* non-diabetics (*P* = 0.02).  No difference in pain intensity in diabetics with MI *vs* non (*P* ≥ 0.05)  Diabetics with UA or MI were more likely to report mid-sternal  chest pain (*P* = 0.04) and chest pain that radiated to the back of the left arm (*P* = 0.01) than non-diabetics  Diabetics with UA or MI reported more SOB (53.1% *vs* 31.3%; NS)  Diabetics with UA or MI, SOB was a factor in deciding to seek care |
| Coronado *et al*[72] | 2541 (1058 women,  410 women with DM); | Secondary analysis  of multisite  a prospective clinical trial / United States | 6.2% of patients with ACS and in 9.8% of AMI. | DM independent predictor of painless presentation in acute MI but not in ACS group. Diabetes more common in non-pain ACS (35% *vs* 26%; *P* = 0.01)  Shortness of breath most common in the painless presentation group (72%) and Women more likely to have painless ACS (53%) (*P* = 0.007) |
| Vaccarino V*et al*[73] | 384878 patients | prospective, observational study/ National Registry of MI/United States | 33% | Atypical presentation patient: older, ↑ proportion of women and diabetics without significant interaction between sex and diabetes was found (*P* = 0.30). andHF comorbidities and less likely coronary intervention with bchance of anticoagulants, aspirin and β blocker usage |
| Canto JG *et al*[74] | 434877 MI pts June 1994-March 1998 | Prospective observational study/ United States | 33% have no chest pain | patients without chest pain on presentation:  Likely to be diabetics (32.6% *vs* 25. 4%)  Older (74.2 *vs* 66.9 yr). Likely to be females (49.0% *vs* 38.0%)  Likely to have prior HF (26.4% *vs* 12.3%).  Had a longer delay before hospital presentation (mean, 7.9 *vs* 5.3 h),  Less likely to be diagnosed with confirmed MI at the time of admission (22.2% *vs* 50.3%).  Less likely to receive thrombolysis or PCI (25.3% *vs* 74.0%), aspirin (60.4% *vs* 84.5%), *B*B (28.0% *vs* 48.0%), or heparin (53.4% *vs* 83.2%).  23.3% in-hospital mortality *vs* 9.3% in patients with chest pain |
| Medalie JH *et al*[75] | 9509 healthy adult subjects | Israeli Heart Attack study, cohort/ Israel | 3.6 unrecognized MI/ 1000 persons and 5.3 clinical ones/ 1000 persons | By multivariate analysis age, left axis deviation, LVH, cigarette smoking, systolic or diastolic Bp, and PVD are the most significant risk factors. cholesterol, **DM**, anxiety, and psychosocial problems, do not play a significant role in unrecognized MI. |
| Brieger D *et al*[76] | 20881 ACS patients | Global Registry of Acute Coronary Events/multinational, prospective, observational study (in 14 countries) | 8.4% presented without chest pain | 23.8% not initially recognized as having an ACS < 33% of the population with atypical symptoms are diabetics.  Less likely to receive effective cardiac medications.  ahospital morbidity and mortality (13% *vs* 4.3%, respectively; *P* < 0.0001).  ahospital mortality rates in patients with presenting symptoms of pre-syncope/syncope. Nausea or vomiting, dyspnea and in those with painless presentations of UA |
| aincrease/higher; bdecreased /lower. MI: Myocardial infarction; UA: Unstable angina; AMI: Acute myocardial infarction; ACS: Acute coronary syndrome; DM: Diabetes mellitus; SOB: Shortness of breath. | | | | |

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| **Table 3 Studies that have not shown that diabetes mellitus is predictor of atypical presentations of Acute coronary syndrome** | | | | |
| **Ref.** | **Study population/** | **study type/ country** | **Atypical presentation %** | **Conclusion** |
| Meshack AF *et al*[77] | 589 patients, ages of 25 and 74 yr, with AMI | a community-based surveillance program/ United States | Sweating (64.2%), fatigue (62.6%), dyspnea (60.3%), and arm or jaw pain (58.2%). | Adjusting for age, DM, gender, and relative to non-Hispanic whites, Mexican Americans more likely to report chest pain, upper back pain, and palpitations, less likely to report arm or jaw pain |
| Richman *et al*[78] | 216 (19 women with  DM); AMI | a prospective, observational study/United States | no statistical difference in diabetics *vs* non-diabetics in terms of the presence chest pain character | No difference in frequency of chest pain or associated symptoms by diabetic status (*P* ≥ 0.05).  -no chest pain symptoms more common in diabetic patients (NS). |
| Kentsch *et al*[79] | 1042 (330 women;  155 women with DM) with STEMI | Secondary analysis  of MITRA PLUS ( 18786 pts.; North German Registry, NGR, 1042 pts.)/ Germany | 16.9% of DM and 15.0% of non-DM | No difference in frequency or intensity of chest pain by diabetic status  Patients with DM reported significantly more dyspnea than those  Without DM (29.5% *vs* 19.5%; *P* < 0.01) |
| DeVon *et al*[80] | 100 (50 women, 23  women with DM); DM | Prospective Secondary analysis; descriptive, cross sectional;  structured  interview  /United States | 3% | No difference in the frequency and severity of chest pain in diabetics *vs*, non-diabetics (*P* ≥ 0.05).  No differences in symptoms of UA by diabetic status.  Patients with DM reported weakness as second most common symptom and more likely to describe chest pain as squeezing (*P* = 0.02) or aching (*P* = 0.04) than non-diabetics.  Diabetics have↑frequency of hyperventilation (*P* = 0.04) and b frequency of nausea (P = 0.04) than non-diabetic. |
| Thuresson *et al*[81] | N = 1939 (480 women,  82 women with DM); | descriptive, cross sectional study/Sweden | See conclusion | No difference in chest pain or other ACS symptoms by DM status  Women reported more tiredness/ weakness, anxiety/fear, vomiting, back pain, left arm painand neck or jaw pain than men (*P* = 0.01). |
| bdecreased /lower. STEMI: St elevation myocardial infarction; UA: Unstable anginal AMI: Acute myocardial infarction; ACS: Acute coronary syndrome; DM: Diabetes mellitus; PVD: peripheral vascular disease. | | | | |