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Atypical presentation of acute and chronic coronary artery disease in diabetics

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Abstract

In patients with diabetes mellitus, cardiovascular disease is the principal cause of mortality and chest pain is the most frequent symptom in patients with stable and acute coronary artery disease. However, there is little knowledge concerning the pervasiveness of uncommon presentations in diabetics. The symptomatology of acute coronary syndrome, which 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 ischemia to a wide spectrum of non-chest pain symptoms. Worldwide, few studies have highlighted this under-investigated subject, and this aspect of ischemic heart disease has also been under-evaluated in the major clinical trials. The results of these studies are highly diverse which makes definitive conclusions regarding the spectrum of atypical presentation of acute and even stable chronic coronay artery disease difficult to confirm. This may have a significant 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 on the atypical presentations in both acute and chronic ischemic heart disease which may give some emphasis to this under-investigated topic.

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

Core tip: Atypical presentations of both acute and chronic ischemic heart disease in diabetic patients is one of the most under-investigated subjects despite extensive research into coronary artery disease even in major clinical trials. To date, according to available data from numerous studies, the impact of atypical presentation on outcome is highly controversial making definitive conclusions difficult. This may have a significant impact on morbidity and mortality of acute and chronic coronary artery disease in diabetics.

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INTRODUCTION

Cardiovascular morbidity is the main cause of death in diabetics. It is predicted that 366 million patients globally will have diabetes mellitus by 2030. As diabetes mellitus progresses, it results in endothelial dysfunction and changes in energy metabolism which lead to atherosclerosis in medium- and large-caliber arteries, creating lesions in coronary, cerebrovascular and peripheral arteries. Additionally, atherosclerotic plaques tend to develop much earlier, advance more swiftly and are more diffuse in diabetic patients than in non-diabetics. These factors

contribute to a two to four-fold higher risk of cardiovascular events in diabetics compared to non-diabetics, with cardiovascular disease being the main cause of death. The combined mortality rate due to cardiovascular disease and diabetes mellitus is 245/100000 population for adults aged 30 to 70 years according to World Health Organization report[1-3].

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

Diabetic patients frequently present with silent myocardial ischemia (SMI), and the absence of an imperative clinical "warning symptom". Statistics from the Framingham study showed that asymptomatic patients with various risk factors have an annual cardiac mortality rate of approximately 3%[4,5,7]. Such outcomes from these studies raise numerous questions regarding diabetes mellitus and CAD: Why is myocardial ischemia repeatedly atypical or silent in diabetic patients? In what way is it discovered? What is its aftermath? How do we deal with it? The current analysis will tackle these issues. We identified studies *via* searches in MEDLINE, PubMed, EMBASE, and Current Contents and by reviewing reference lists in all the studies performed in the last 30 years from both developed and developing countries using the following keywords: diabetes mellitus, acute coronary syndrome (ACS), acute myocardial infarction (AMI), ischemic heart disease, atypical presentation, and SMI. We attempted to provide conclusions and future perspectives on this under-evaluated topic according to up-to-date studies from different parts of the world.

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

Chest pain is the cornerstone symptom of ACS. However, data concerning the prevalence of 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 a wide range of atypical presentations which makes the diagnosis of CAD challenging. In addition, diabetic patients with CAD have poorer 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 degree of CAD in diabetics, the magnitude of left ventricular remodeling, and the occurrence of significant ventricular dysrhythmias[8-27].

Despite the fact that CAD is the primary vascular complication of diabetes, there is a significant gap in our knowledge and understanding on atypical ACS symptoms in diabetics. Conventional risk factors, such as, hypertension, diabetes, hypercholesterolemia and smoking have a significant impact on the symptomatology of ACS and stable angina, including both pain and non-pain symptoms. Although numerous investigations on diabetes management have been performed, only a few studies have focused on atypical ACS symptoms in patients with diabetes with contradictory results. Diabetics may have a diminished awareness of ischemic chest pain which could result in an uncharacteristic presentation. This may be explained by autonomic neuropathy and prolongation of the anginal perceptual threshold[28]. In addition, diabetic patients with SMI have evidence of a disseminated abnormality in metaiodobenzylguanidine uptake on positron emission tomography. A similar finding was also observed in asymptomatic diabetic patients on stress testing with a dipyridamole stress myocardial scan and contrast echocardiography in approximately 60% of diabetic patients, these findings reflect abnormal pain perception interrelated with sympathetic denervation[29]. SMI is seen more frequently in diabetic patients than in the general population. SMI may be the main atypical presentation observed 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 the patient population investigated. The prevalence of silent CAD is 6%-23% in low-risk diabetics, and can be as high as 60% in high-risk diabetic patients. Recently it was recognized that silent CAD has a similar prognosis and adverse events rate when compared with symptomatic CAD[31]. Possible explanations for the dissimilar symptoms in patients with diabetes mellitus, comprise 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 that patients with symptomatic autonomic neuropathy are at increased risk of sudden death; however, it still controversial whether there is adequate scientific data available to indicate 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 few 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 evidence is available concerning the morbidity and mortality of diabetic patients managed with insulin *vs* oral hypoglycemic agents or diet after AMI[12,18,27,32,33]. Similarly, uncertainty still exists regarding the negative prognostic implications of diabetes in patients with a different spectrum of ACS *i.e.*, unstable angina, non-ST and ST-segment elevated 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 infarction/ischemia (SMI) is more frequent than formerly thought. Up to 25% of patients with CAD have suffered silent SMI; the magnitude of the myocardium affected is on average 10% of the left ventricle muscle mass, and it is more prevelant in diabetics. The phenomenon of SMI is still debatable. The 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 a 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. One thousand six hundred and twenty-one patients were registered in the derivation cohort and 338 patients in the validation cohort. SMI was 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 (OR = 1.5; 95%CI: 1.1-1.9; P = 0.004). In the validation cohort, the prevalence of SMI was 26.3%, with a 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].

In a cross-sectional study involving 200 subjects (mean age; 46 ± 10 years, 31 had diabetes), the subjects underwent an exercise stress test. A positive test for silent ischemia was seen in 19% of diabetics and 13% of non-diabetics, which was not statistically significant (P = 0.397). Hypertension and obesity were found more frequently in diabetics (48% *vs* 27% and 35% *vs* 18%, respectively)[37]. Blood lipid levels may predict SMI in non-insulin dependent diabetes. A study included 220 asymptomatic diabetics who underwent laboratory tests and gated single-photon emission computed tomography with coronary angiography as the confirmatory test, when gSPECT detected ischemia. A higher level of total cholesterol was seen in gSPECT-positive diabetics, together with 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. This study included more men (33.3%) than women (24.8%). HDL levels were significantly lower in these patients. The association between low HDL and 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 a high combination of cardiovascular risk factors detected SMI in a significant proportion of patients and this seemed to be related to future coronary events. Diabetic nephropathy may indicate a greater likelihood of abnormal studies[39].

A study evaluated the pervasiveness of SMI in 147 subjects in a diabetic Afro-Caribbean population. 23.1% had SMI; these patients had a personal history of cardiovascular disease similar to those without diabetes. On multivariate logistic-regression analyses, the adjusted odds ratio of SMI was 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 for detecting SMI, especially in diabetic patients at high cardiovascular risk. A study of 79 diabetics (average age = 58.8 ± 11.8 years) revealed that 67.1% had a positive test, with a predominance of motion abnormalities in the 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) were the main cardiovascular risk factors associated with positivity[41].

In the detection of ischemia in asymptomatic diabetics (DIAD) study, the largest prospective study with a 4.8-year follow-up period included 1123 asymptomatic persons with type 2 diabetes who were randomized to either testing with stress myocardial perfusion scan or no testing. In this study, 53%-75% of participants with intermediate to high cardiovascular risk had a prevalence of inducible ischemia on screening that ranged from 21% to 24%, which was almost comparable to lower-risk patients (19%-23%). Patients with intermediate-/high-risk had higher rates of cardiac events (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 the high-risk UKPDS group (approximately 2% per year). Surprisingly the annual cardiac event rate for intermediate/high risk was low and not altered by standard testing for inducible ischemia[42].

High LDL level and higher carotid intima-media thickness are predominant issues that can indicate whether a patient with non-insulin dependent diabetes (NIDDM) is are at risk of SMI. A high carotid intima-media thickness is a substitute and dependable indicator of higher risk of CAD in non-insulin dependent diabetic patients, even in those without evident CAD[43].

Another study determined SMI in 90 unselected middle-aged asymptomatic NIDDM patients (48 men; mean age: 49 ± 6 years, mean diabetes duration of 4 ± 4.2 years (range 1-21 years) without CAD as documented by treadmill exercise test. Four percent of patients had a positive test. Diabetics with SMI were older (55 ± 3

years *vs* 49 ± 6 years, $P = 0.04$), had a higher fibrinogen level (372 ± 51 *vs* 307 ± 71 mg/dL, $P = 0.04$) and had lower total exercise time and peak workload (375 ± 30 s *vs* 474 ± 115 s, $P = 0.04$; 7.3 ± 0.5 *vs* 8.9 ± 1.9, $P = 0.04$, respectively). Insulin resistance is related to different atherosclerosis risk factors. Exercise test outcomes showed increased cardiac sympathetic activity and parasympathetic withdrawal in increased insulin resistance[44]. Left atrial surface area independently predicted SMI after adjustment for established echocardiographic and inflammatory risk factors in diabetics[45]. Age and differential pulse pressure may be predictors of SMI[46].

A study estimated the frequency of SMI in 353 asymptomatic Caucasian diabetic patients using the treadmill test with single-photon emission computed tomography and exercise testing or dipyridamole injection with coronary angiography as the confirmation test. Patients with SMI (8.5% were diabetics: 3 IDDM and 13 NIDDM) were older and had autonomic neuropathy, hypertension, dyslipidemia and higher microalbuminuria (613 ± 211 mg/d *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. A total of 1123 patients, with no known or suspected CAD were randomly assigned to either stress testing and 5-year clinical follow-up or to follow-up only. In this study 22% had SMI; the strongest prognosticators for abnormal tests were abnormal Valsalva, male sex, and diabetes duration, but not traditional cardiac risk factors or inflammatory and prothrombotic markers. Choosing only patients who met the American Diabetes Association guidelines failed to detect 41% of patients with SMI[48]. Erectile dysfunction may become a possible indicator to identify diabetic patients with SMI during screening, 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 to detect SMI, significant CAD was identified in 9% of asymptomatic diabetics. Dynamic left ventricular outflow obstruction was detected in 59% of diabetics and in only 22% of non-diabetics, however, these results need to be investigated in future studies[51].

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

A few other studies[55-65] assessed different aspects of the association between SMI and diabetes (Table 1). Patients with SMI had higher ischemia in the working forearm compared 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, diabetic neuropathy which 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 the absence of pain[59,60].

ATYPICAL PRESENTATION OF ACUTE CORONARY SYNDROME IN DIABETICS

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

Studies which have shown diabetes mellitus is a predictor of the atypical presentation of acute coronary syndrome (Table 2)

In a nation-wide survey conducted in 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 in 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 a multivariate analysis, variables linked with no anginal pain/atypical symptoms on presentation were: history of heart failure, age, lack of past angina, diabetes, and non-smoking. ST-elevation was inversely associated with no anginal pain/atypical symptoms on admission (OR = 0.48; 95%CI: 0.37-0.63)[68].

A study by Culić *et al*[69] who performed subgroup analyses showed that diabetes was an independent prognosticator of "atypical" presentation of AMI in women. In this prospective, observational study of a large number of symptoms in 1996 patients, it was established that chest pain was more often reported by males, smokers, and hypertensive, non-diabetic, and hypercholesterolemic patients. Women frequently reported 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 were diabetes mellitus ($P = 0.0002$ and $P = 0.002$,

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 of SMI = 26.3% (n = 89), while the prevalencea in diabetics (35.8%) *vs* non-diabetics was 24% (P = 0.049)
Sheikh *et al*[37]	200 subjects, 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 *et al*[38]	220 asymptomatic NIDDM patients	A prospective, observational, analytical study /Havana	29.10%	Type 2 diabetics with ischemia had ↑ levels of total cholesterol, LDL and triglycerides. HDL levels were significantly ↓. The association of ↓ HDL with ↑ triglycerides was a strong indicator of SMI in NIDDM patients
Ruano Pérez *et al*[39]	56 asymptomatic diabetics	retrospective study	46.40%	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 *et al*[40]	147 NIDDM patients	cross-sectional study /France	23.10%	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 *et al*[41]	79 diabetics	Prospective/France	67.10%	Predominance of motion abnormalities in the anterior territory (83%). Cardiovascular risk factors associated with positivity of the test were 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 *et al*[42]	1123 NIDDM patients	Prospective/Detection of Ischemia in Asymptomatic Diabetics (DIAD) /United States and Canada (DIAD) study	21%-24% in the intermediate high risk group 19%-23% in the low risk group	Cardiac event rates ↑ in intermediate/high-risk. The annual cardiac event rate was ≤ 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 *et al*[43]	77 NIDDM	Prospective study/ India	28.90%	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 was found to be statistically significant between the silent CAD and non-CAD groups (P = 0.019)
Ugur-Altun *et al*[44]	90 asymptomatic NIDDM patients	Prospective/Turkey	4%	Diabetics with SMI had ↑ fibrinogen level (372 ± 51 mg/dL *vs* 307 ± 71 mg/dL, P = 0.04), had ↓ total exercise time and peak workload (375 ± 30 s *vs* 474 ± 115 s, P = 0.04; 7.3 ± 0.5 *vs* 8.9 ± 1.9, P = 0.04, respectively)
Chico *et al*[47]	353 NIDDM asymptomatic Caucasians	Prospective/Spain	8.50%	SMI patients were older, had ↑ prevalence of autonomic neuropathy, microalbuminuria, hypertension, and dyslipidemia than those without
Wackers *et al*[48]	1123 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 were not predictive. Ischemic adenosine-induced ST-segment depression with normal perfusion in women
Falcone *et al*[50]	618 patients with CAD	Prospective/Italy	58%	SMI during exercise seen in 58% of diabetics and 64% of nondiabetics. Both diabetics and non-diabetics with exertional SMI had ↑ 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 *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 in only 22% in the non-diabetic population
Sukhija *et al*[53]	30 diabetics/30 non diabetics	Prospective/India	46.70%	Diabetics had ↑ heart rate and a greater number of supraventricular and ventricular ectopics, ↑ prevalence of multi-vessel involvement and diffuse disease compared to controls. 50% of diabetics and none of the controls had autonomic dysfunction. Autonomic dysfunction was present in 85.7% of diabetics with SMI *vs* 18.7% of diabetics without SMI (P = 0.001)
May *et al*[54]	240 diabetics	Prospective/Denmark	13.50%	Frequency of SMI did not differ significantly between diabetics and non-diabetics. Systolic blood pressure was predictive of SMI in diabetes
Tamez-Pérez *et al*[55]	60 NIDDM patients	Prospective/ Spain	17%	In a 2-yr follow-up, 4 diabetics developed symptomatic angina pectoris

Ahluwalia *et al*[56]	20 male diabetics	Prospective/India	50%	On exercise testing in diabetics, SMI was 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 non-diabetic patients with three-vessel disease ($P < 0.05$) and in none of the patients with two- or one-vessel disease
Tanaka *et al*[61]	92 NIDDM patients	Prospective / Japan	38%	Diabetics with positive treadmill test were smokers, and had hypertension and ↑ triglyceride level compared to treadmill negative diabetics
Nesto *et al*[62]	30 diabetics with peripheral vascular disease	Prospective /United States	57%	57% had thallium abnormalities, with reversible thallium defects compatible with ischemia in 47% and evidence of prior, clinical SMI in 37%. Thallium abnormalities were seen more frequently in diabetics with concomitant hypertension and cigarette smoking ($P = 0.001$)
Koistinen *et al*[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 *et al*[64]	52 IDDM and 87 NIDDM 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 ↑ than the general population
Touze *et al*[65]	50 black African diabetics	Prospective /Africa	10%	SMI was ↓ among black African diabetics compared with white diabetics. The coronary lesions were mostly limited. Proximal narrowing and one-vessel disease mostly encountered-

↑: Increase/higher; ↓: Decreased/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

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 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 was the predictor of atypical presentation[69].

A recent study in South Korea evaluated the risk factors associated with atypical presentation according to age. In this study, diabetes and hyperlipidemia predicted atypical symptoms in the younger (< 70 years) age group. Comorbid illnesses such as stroke or chronic obstructive pulmonary disease were positive predictors in the older (> 70 years) age group[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 long-established ACS was made in 24% of patients, of which 35% had AMI and 65% had unstable angina. Sixty-two percent of ACS patients and 9.8% of AMI patients had no pain. Patients with painless ischemia were 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 infarction, logistic regression predicting lack of pain categorized age, heart failure and diabetes as the main predictors with only age and heart failure in those with ACS. After controlling for clinical features, silent acute ischemia predicted augmented hospital mortality[72].

In the National Registry of Myocardial Infarction 2 (NRMI 2): a prospective observational study in the United States, which included 434877 patients with MI, 33% had no chest pain on presentation to the hospital and were 7 years older than those with chest pain (74.2 years *vs* 66.9 years), more likely to be female (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 h). These patients were less likely to be diagnosed with SMI and were less likely to undergo thrombolysis or primary angioplasty (25.3% *vs* 74.0%), and treatment with aspirin (60.4% *vs* 84.5%), beta-blockers (28.0% *vs* 48.0%), or heparin (53.4% *vs* 83.2%). SMI 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 in developed and developing countries have 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 who had an average annual incidence of 3.6/1000 persons with unrecognized infarcts and 5.3/1000 persons with clinical infarcts. Patients whose electrocardiograms were initially read by cardiologists as non-infarcts, but by the computer as infarcts, had a high rate of unrecognized infarcts in the subsequent 5 years and a markedly higher 7-year mortality rate in the unrecognized infarct group *vs* the 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 were significant risk factors for unrecognized myocardial infarction on multivariate analysis. Cholesterol, diabetes, anxiety, and psychosocial problems, do not play a significant role in unrecognized infarcts[75].

The Global Registry of Acute Coronary Events (GRACE study), is the largest multinational, prospective,

Table 2 Studies which have shown that diabetes mellitus is a predictor of atypical presentation 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% had no chest pain	In multivariate analysis, variables associated with no anginal pain/atypical symptoms on presentation (in ↓ order): history of heart failure, age, no past angina, diabetes and non-smoking. 18.7% of male patients had no chest pain on presentation vs 29.7% of females
Culić *et al*[69]	1996 MI patients	A prospective, observational study/ Croatia	14.8% had no chest pain	The independent predictors of atypical presentation in both gender; ↓ levels 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), and no smoking in men ($P = 0.005$)
				The independent predictors of the presence of non-pain symptoms; DM ($P = 0.048$ and $P = 0.005$, respectively), ↑ levels of CK-MB ($P = 0.01$ and $P = 0.049$, respectively) and hypercholesterolemia (P =0.01) in both men and 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 gender and ACS type indicated that diabetes and hyperlipidemia significantly predicted atypical symptoms in 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-diabetics ($P \geqslant 0.05$)
				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)
				In 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 the 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 were more likely to have painless ACS (53%) ($P =$ 0.007)
Vaccarino *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 a significant interaction between sex and diabetes ($P = 0.30$). HF comorbidities and less likely to have coronary intervention with ↓ chance of anticoagulants, aspirin and β blocker usage
Canto *et al*[74]	434877 MI ptsJune 1994-March 1998	Prospective observational study United States	33% had no chest pain	Patients without chest pain on presentation:
				Likely to be diabetics (32.6% *vs* 25. 4%)
				Older (74.2 yr *vs* 66.9 yr). Likely to be female (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 h *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%), BB (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 *et al*[75]	9509 healthy adult subjects	Israeli Heart Attack study, cohort/ Israel	3.6 unrecognized MI/ 1000 persons and 5.3 clinical MI/1000 persons	By multivariate analysis, age, left axis deviation, LVH, cigarette smoking, systolic or diastolic BP, and PVD were the most significant risk factors. Cholesterol, DM, anxiety, and psychosocial problems, do not play a significant role in unrecognized MI
Brieger *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 were diabetics.
				Less likely to receive effective cardiac medications
				↑ hospital morbidity and mortality (13% *vs* 4.3%, respectively; $P < 0.0001$)
				↑ hospital mortality rates in patients with presenting symptoms of pre-syncope/syncope. Nausea or vomiting, dyspnea and in those with painless presentations of UA

↑: Increase/higher; ↓: Decreased/lower. MI: Myocardial infarction; UA: Unstable angina; AMI: Acute myocardial infarction; ACS: Acute coronary syndrome; DM: Diabetes mellitus; SOB: Shortness of breath.

Table 3 Studies which have not shown that diabetes mellitus is a predictor of atypical presentation of acute coronary syndrome

Ref.	Study population/	Study type/country	Atypical presentation %	Conclusion
Meshack *et al*[77]	589 patients, aged 25 to 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 were more likely to report chest pain, upper back pain, and palpitations, and 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	No difference in the frequency of chest pain or associated symptoms by diabetic status ($P \geq 0.05$); No chest pain symptoms was 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 the 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	rospective 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 ($P \geq 0.05$) No differences in UA symptoms by diabetic status Patients with DM reported weakness as the 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 had ↑ frequency of hyperventilation ($P = 0.04$) and ↓ frequency of nausea ($P = 0.04$) than non-diabetics
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 pain and neck or jaw pain than men ($P = 0.01$).

↑: Increase/higher; ↓: Decreased/lower. STEMI: ST elevation myocardial infarction; UA: Unstable angina AMI: Acute myocardial infarction; ACS: Acute coronary syndrome; DM: Diabetes mellitus; PVD: Peripheral vascular disease.

observational study and involves 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 included, 8.4% had no chest pain, and 23.8% were not initially recognized as having ACS. These patients had higher hospital morbidity and mortality (13% *vs* 4.3%, respectively; $P < 0.0001$) and were less likely to receive effective cardiac medications than patients with typical presentation. After adjusting for potentially confounding variables, excluding diaphoresis, higher in-hospital mortality rates were seen in patients who presented with pre-syncope/syncope (OR = 2.0; 95%CI: 1.4-2.9), nausea or vomiting (OR = 1.6; 95%CI: 1.1-2.4), and dyspnea (OR = 1.4; 95%CI: 1.1 to 1.9), than in those with painless presentations of unstable angina (OR = 2.2; 95%CI: 1.4-3.5) and ST-segment elevation MI (STEMI) (OR = 1.7; 95%CI: 1.2-2.2). In patients with unstable angina and non-ST elevation MI, 5.7% and 12.3% had atypical symptoms, respectively. In addition, patients with atypical presentation had less coronary angiography and subsequent revascularization, anticoagulant, antiplatelet and B-blocker therapy. These patients were also less likely to receive aspirin, B-blockers, or statins after discharge, this was seemingly linked to the failure to identify the diagnosis initially. Bearing in mind the higher baseline risk of the population presenting without chest pain, those with atypical presentation frequently had in-hospital complications. On the other hand, the excessive mortality rate seen in the GRACE study was marked with almost 20% in-hospital mortality in the silent STEMI patients. Nevertheless, the absence of chest pain resulted in a greater probability of in-hospital death in all patients with ACS, and, even after multivariate analysis, the excessive mortality rate persisted among patients with unstable angina and STEMI[76].

Studies which did not show that diabetes mellitus is a predictor of atypical presentation of acute coronary syndrome (Table 3)

Numerous studies[77-81] have shown that diabetes mellitus is not a predictor of atypical presentation of ischemic syndrome. A study examined the disparities between Mexican Americans and non-Hispanic whites in the described symptoms of AMI. The symptoms in patients in a community-based surveillance program were determined 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 having either definite or possible AMI (aged 25 to 74 years) was obtained. Chest pain was the most frequent complaint (83.2%), followed by 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 were less likely to report arm or jaw pain. Similarly, women predominantly reported fatigue, dyspnea, dizziness, upper back pain, palpitations, and cough, but less frequently reported chest pain. Substantial differences were observed in older compared to younger patients' symptoms[77].

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

Data from 2 registries of AMI patients presenting in hospital (MITRA PLUS with 18786 patients; North German Registry, NGR), analyzed AMI symptoms in 1042 diabetic and non-diabetic patients. Diabetics were significantly older and more often female than non-diabetics. No difference in the incidence of pre-infarction angina between the 2 groups (Mitra Plus) was observed. In the NGR, severe angina during AMI was perceived in 49.8% of diabetics *vs* 46.3% of non-diabetics (P = NS). In addition, 16.9% of diabetics and 15.0% of non-diabetics (P; NS) had 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 differences in the clinical symptoms of AMI patients with and without diabetes mellitus were noted. Silent or minimally symptomatic AMI was more common in non-diabetics[79]. A study determined the differences in symptoms 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%), had a past cardiac history (85% *vs* 65%), and prior angiogram (85% *vs* 67%). Diabetics had less nausea (20% *vs* 40%), less squeezing (25% *vs* 48%) and less aching (25% *vs* 45%) pain, with more frequent hyperventilation as the presenting symptoms (27.5% *vs* 11.7%). With no difference in other cardiac symptoms seen in the two groups[80].

SILENT AND ATYPICAL MYOCARDIAL ISCHEMIA IN DIABETICS: TO SCREEN OR NOT?

Assuming a greater risk of cardiovascular events and more frequent silent CAD in diabetics compared to non-diabetics, screening asymptomatic diabetic patients for CAD is an attractive concept. Nevertheless, there are many elements against instigating a wide-ranging screening program. Of note is the paucity of confirmed data indicating that a prospectively utilized screening program has a positive prognostic impact in asymptomatic diabetic patients. From the above reviewed studies the incidence of atypical SMI is highly variable. Measures should be taken to manage 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 which used stress single-photon emission computed tomography imaging showed around 50% abnormal images and 20% high-risk images, respectively. However, the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study[42] described a considerably 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 investigate silent and/or atypical myocardial ischemia and this applies to stable CAD in high risk diabetic patients, *i.e.*, patients with long-standing diabetes and diabetic complications such as diabetic neuropathy which may frequently present atypically. We suggest using a test which has high specificity and sensitivity for the detection of myocardial ischemia such as a myocardial perfusion scan and SPECT scan as shown in the above studies. The massive fiscal consequences of investigating all asymptomatic diabetic patients at intermediate and high risk using clinical scoring systems should be considered. Undoubtedly more investigations are required to address these issues.

CONCLUSION

Not all diabetics have the same coronary risk, therefore, it is important to determine which investigations to perform and for which patients. This strategy is reasonable as it allows identification of patients who require a medical or an invasive (angioplasty *vs* CABG) procedure, 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 exercise stress testing is sub-maximal or non-diagnostic, a second investigation with perfusion myocardial scintigraphy may be warranted bearing in mind that in 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 scintigraphy.

The greater incidence of SMI in diabetics seems to be due to the increased frequency of ischemic heart disease in diabetics. The importance of cardiac autonomic neuropathy in SMI is still debatable, but is the most acceptable cause of SMI, as discussed in the 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, and peripheral occlusive arterial disease. Upcoming studies should determine possible approaches to augment the patient subgroup that will possibly benefit from screening with judicious cost-effective analyses. Currently, there are no data to support the use of anti-ischemic medication to improve CAD in diabetic patients.

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