

## PERIPHERAL NEUROPATHY AND CLINICAL SIGNS OF ACUTE CORONARY SYNDROME IN PATIENTS WITH DIABETES MELLITUS

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**ABSTRACT:** This study aimed to assess the severity of peripheral neuropathy in diabetic patients with acute coronary syndrome and its association with the severity of clinical signs. Prospective, cross-sectional and quantitative study. Data were collected from November 2015 to February 2016 in a hospital in the city of São Paulo. The clinical signs of diabetic patients with acute coronary syndrome were analyzed and the intensity of peripheral neuropathy was assessed using the Neuropathic Symptom Score (NSS). Fifty patients were assessed, and 33 (66%) participants had precordial catch syndrome, as well as sweating and dyspnea. Neuropathic symptoms were also identified in 33 (66%) patients, and there was no association between intensity of neuropathy and intensity of clinical signs of acute coronary syndrome. The clinical assessment of diabetic patients with acute coronary syndrome by nurses should be very careful, especially in patients with atypical clinical signs, depending on the degree of peripheral neuropathy.

**DESCRIPTORS:** Diabetes Mellitus; Acute coronary syndrome; Precordial pain; Diabetic neuropathies; Infarction.

### NEUROPATIA PERIFÉRICA E SINAIS CLÍNICOS DE SÍNDROME CORONARIANA AGUDA EM PACIENTES COM DIABETES MELLITUS

**RESUMO:** Objetivou-se avaliar o nível de neuropatia periférica em pacientes diabéticos com síndrome coronariana aguda e sua associação com a intensidade dos sinais clínicos. Estudo prospectivo, transversal e quantitativo. Os dados foram coletados de novembro de 2015 a fevereiro de 2016 em um hospital na cidade de São Paulo. Foram analisados os sinais clínicos apresentados pelos pacientes com síndrome coronariana aguda portadores de diabetes *mellitus* e o nível de neuropatia periférica pela Escala de Sintomas Neuropáticos. Foram avaliados 50 pacientes, apresentaram dor precordial em aperto em 33 (66%) participantes, além da sudorese e dispnéia. Sintomas neuropáticos foram identificados em 33 (66%) pacientes, não observada associação entre o nível de neuropatia e a intensidade dos sinais clínicos da síndrome coronariana aguda. A avaliação clínica realizada pelo enfermeiro em pacientes diabéticos com síndrome coronariana aguda deve ser feita de forma rigorosa, principalmente nos pacientes que podem apresentar sinais clínicos atípicos dependendo do grau de neuropatia periférica.

**DESCRIPTORIOS:** Diabetes *Mellitus*; Síndrome coronariana aguda; Dor precordial; Neuropatias Diabéticas; Infarto.

### NEUROPATÍA PERIFÉRICA Y SIGNOS CLÍNICOS DE SÍNDROME CORONARIO AGUDO EN PACIENTES CON DIABETES MELLITUS

**RESUMEN:** El objetivo fue evaluar el nivel de la neuropatía periférica en los pacientes diabéticos con síndrome coronario agudo y su asociación con la gravedad de los signos clínicos. Un estudio prospectivo, transversal y cuantitativo. Los datos fueron recolectados a partir de noviembre 2015 a febrero 2016 en un hospital de Sao Paulo. Se analizaron los signos clínicos observados en pacientes con síndrome coronario agudo, diabetes mellitus y el nivel de los síntomas Neuropatía periférica Neuropatía Scale. Se analizaron 50 pacientes tenían dolor en el pecho en 33 (66%) participantes, así como la sudoración y la disnea. síntomas neuropáticos se identificaron en 33 (66%) pacientes, y no hay asociación entre neuropatía y el nivel de intensidad de los signos clínicos de síndrome coronario agudo. La evaluación clínica llevada a cabo por la enfermera en pacientes diabéticos con síndrome coronario agudo debe realizarse con precisión, en particular en pacientes que pueden tener signos clínicos atípicos en función del grado de la neuropatía periférica.

**DESCRIPTORIOS:** Diabetes Mellitus; síndrome coronario agudo; dolor en el pecho; neuropatías diabéticas, infarto.

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## ● INTRODUCTION

Deficient insulin secretion by the pancreas, or its insufficient action on the target tissues, which causes hyperglycemia<sup>(1)</sup>. Untreated, DM can lead to complications over time, especially visual impairment, kidney failure, limb amputations, neuropathies and higher incidence of cardiovascular diseases such as myocardial infarction<sup>(2-3)</sup>.

DM affects cell functions, particularly endothelial cells, smooth muscle cells and thrombocytes<sup>(4)</sup>, and endothelial dysfunction is the first pathophysiological precursor for the onset of atherosclerosis, which causes inflammation, thrombosis, arterial stiffness and decrease in vascular tone and blood flow<sup>(5-7)</sup>.

The cardiovascular diseases of diabetic patients are more complex because the coronary arteries in diabetic patients are narrower than normal, increasing the probability of multiple lesions and with lower efficacy of percutaneous myocardial revascularization<sup>(8)</sup>.

One of the main presentations of coronary artery disease is Acute Coronary Syndrome (ACS), which can be identified by the following signs and symptoms: oppressive pain in the precordial region that can radiate to the jaw and upper limbs and be associated with dyspnea, palpitation, weakness, fatigue, dizziness, sweating, nausea and vomiting. The presence of these clinical signs must be detected to accelerate patient care. Delay in the identification of these symptoms may aggravate the patient's conditions<sup>(9-10)</sup>.

Some patients, especially those with DM, may present atypical clinical signs, i.e., absence of classic symptoms, such as precordial pain, and/or less intense pain. Delayed diagnosis of DM may delay appropriate treatment, increasing mortality rates<sup>(11)</sup>.

These atypical signs in DM patients are probably related to peripheral neuropathy, because chronic hyperglycemia can reduce the perception of pain and prolong the anginal threshold<sup>(12)</sup>. In a study with a population of 13,043 individuals with type 2 diabetes aimed to verify the association of peripheral neuropathy (PN) with the prevalence of cardiovascular events, a prevalence of 1,291 (9.9%) patients with PN was identified. Elderly hypertensive individuals who smoked and had neuropathy were more susceptible to cardiovascular diseases. Throughout the study, 5% of PN individuals were found to have cardiovascular events compared to a 2.8% rate of cardiovascular events in individuals without PN<sup>(13)</sup>.

Diabetic patients with atherosclerosis have been the subject of several studies aimed to assess the most appropriate protocol for risk stratification in order to reduce complications in the acute phase<sup>(8-12,14-18)</sup>.

Due to the difficulty in diagnosing DM patients because of the presence of atypical signs secondary to peripheral neuropathy, the use of tools that facilitate the identification of these conditions or that can stratify the risks of mortality/complications of these conditions is strongly recommended. Patients. However, no studies associating the intensity of neuropathy to the intensity of clinical signs of ACS were found. Therefore, this study aimed to verify the intensity of peripheral neuropathy in patients with DM and ACS and assess the association between the intensity of peripheral neuropathy in patients with DM and the intensity of the clinical signs of Acute Coronary Syndrome.

## ● METHOD

Prospective cross-sectional study with exploratory and quantitative approach. Convenience sampling was used and data was collected from November 2015 to February 2016, at cardiology inpatient units, emergency room and hemodynamic units of a large teaching hospital in the city of São Paulo.

The sample included patients over 18 year old with an admission diagnosis of ACS, previously diagnosed with diabetes mellitus, regardless of the type of treatment used and the time of diagnosis. Patients with cardiogenic shock during admission, cognitive deficits and difficulties in verbal communication were excluded from the study. The patients' medical charts were first analyzed by the researcher for identification of those who met the inclusion criteria. Subsequently, the selected

patients were contacted and signed the informed consent form after approval by the Research Ethics Committee.

The research instruments were applied in one day, and sociodemographic and clinical data (personal and family history, risk factors for cardiovascular disease, medications used, time of diagnosis, type of chest pain, pain intensity, duration of pain considering the onset of pain until hospital admission, nausea, vomiting, dyspnea, heartburn, sweating and cough) were analyzed.

In order to assess the intensity of peripheral neuropathy, we used the Neuropathic Symptom Score (NSS) translated and validated into Brazilian Portuguese<sup>(18)</sup>. The instrument has six questions and scores ranging from 3 to 9 points. Neuropathy degree is classified as mild (score 3-4), moderate (score 5-6), and severe when the score is higher than seven<sup>(18)</sup>.

Descriptive statistical analysis and association tests were performed using the Statistical Package for Social Sciences (SPSS), version 19. Quantitative data were presented as means, minimum and maximum values, standard deviation, and the absolute values and frequency were calculated to obtain the qualitative variables. The data were considered statistically significant when  $p$  values  $<0.05$  were obtained in association tests.

## ● RESULTS

During data collection, 160 patients with ACS were admitted to the institution. Of this total, 50 (31.5%) had been diagnosed with DM and were included in the study. Of these, 33 (66%) were males, with a mean age of 58 years and a low educational level. The most frequent medical history included systemic arterial hypertension, dyslipidemia and smoking, according to the following distribution: 44 (88%), 29 (58%), 23 (46%) patients, respectively. The most common type of SCA was acute myocardial infarction with ST segment elevation (STEMI) diagnosed in 28 (56%) patients, in which 82.5% of the cases were in Killip I of severity, as shown in Table 1.

Table 1 – Socio-demographic and clinical characterization. São Paulo, SP, Brazil, 2016 (continues)

Indicator	Variable	N (%)
Genre	Male	33 (66)
	Female	17 (34)
Education	Illiterate	4 (8)
	Incomplete primary school	20 (40)
	Complete primary school	6 (12)
	Incomplete secondary school	9 (18)
	Complete secondary school	7 (14)
	Incomplete higher education	1 (2)
	Complete higher education	2 (4)
	Postgraduate	1 (2)
Age	Average	58
	Standard deviation	10.14
	Min - Max.	35--84
Marital status	Not married	5 (16.7)
	Married	20 (66.7)
	Divorced	3 (10)
	Widowed	2 (6.7)
Patient history	Systemic Arterial Hypertension	44 (88)
	Dyslipidemia	29 (58)
	Obesity	11 (22)
	Acute Kidney Injury	1 (2)

Patient history	Cerebral vascular accident (CVA)	6 (12)
	Heart Failure (HF)	3 (6)
	Alcohol consumption	2 (4)
	Smoking	23 (46)
Medical diagnosis	Unstable Angina	16 (32)
	Acute myocardial infarction without ST segment elevation	6 (12)
	Acute myocardial infarction with ST segment elevation	28 (56)

Regarding diabetes mellitus, there was a total prevalence of type 2 diabetes, with an average time of diagnosis of 114 months, since most glucose values were abnormal, and the mean fasting blood glucose was 281 mg/Dl.

Regarding clinical signs, according to Table 2, the most common precordial pain was precordial catch syndrome identified in 33 (66%) patients, followed by burning pain in 13 (26%). Pain intensity had an average score of 8.1 and the mean duration of pain before seeking the emergency service was 203.1 minutes.

Table 2 – Characterization of clinical signs upon admission. São Paulo, SP, Brazil, 2016

Indicator	Description	N (%)
Precordial pain	Painless	2 (4)
	Catch (stitch)	33 (66)
	Stabbing	2 (4)
	Improvement with change of decubitus	0
	Burning	13 (26)
	Worsened by Palpation	0
	Epigastric region	0
Radiation	Left upper limb (LUL)	16 (32)
	Right upper limb (RUL)	10 (20)
	Jaw	7 (14)
	Back	12 (24)
	Gastric region	3 (6)
	Without radiation	16 (32)
Associated Symptoms	Nausea	18 (36)
	Vomiting	17 (34)
	Dyspnea	26 (52)
	Dry cough	1 (2)
	Productive cough	1 (2)
	Sweating	33 (66)
Intensity of pain	Average	8.1
	Minimum	3
	Maximum	10
	Standard deviation	1.7
Duration of pain (min)	Average	203.1
	Minimum	10
	Maximum	840
	Standard deviation	192

The results of coronary angiography of the patients were as follows: 34 (68%) patients with anterior descending artery stenosis, followed by 24 (48%) patients with right coronary artery obstruction, and 20 (40%) with circumflex artery stenosis.

Assessment of the study patients using the Neuropathy Symptoms and Signs Pain Scale, shown in Figure 1, identified 33 (66%) patients with some degree of neuropathy and 16 (32%) patients with no degree of neuropathy. Of the patients with some degree of neuropathy, 16 (32%) had mild neuropathy, 13 (26%) moderate neuropathy and five (10%) had severe neuropathy.

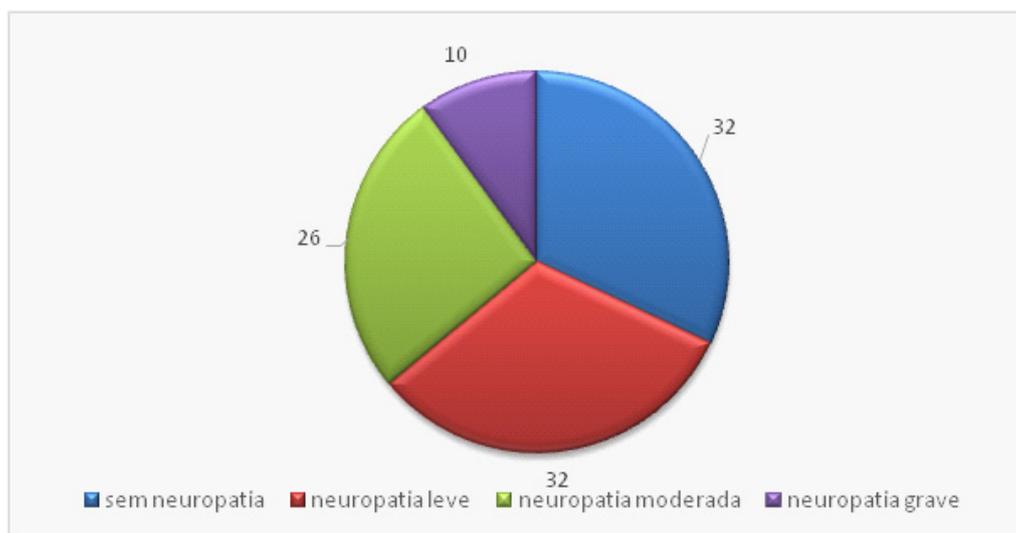


Figure 1 – Distribution of peripheral neuropathy according to the Neuropathic Symptom Score (NSS) (%). São Paulo, SP, Brazil, 2016

Of the patients who had some degree of neuropathy, 34 (68%) patients experienced some type of discomfort or pain in the lower limbs; 19 (38%) patients reported fatigue, cramp or itching; 28 (56%) patients reported lower leg pain with most reports of discomfort in the legs occurring only during the day for 12 (24%) patients; 18 (36%) patients reported awakening during the night due to pain or discomfort, and 23 (46%) patients said the symptoms are relieved when they sit down or lie down.

Table 3 - Frequency of neuropathic symptoms assessed by the Neuropathy Symptom Score. São Paulo, SP, Brazil, 2016 (continues)

Indicator	Description	N (%)
Have you experienced pain or discomfort in your legs?	Yes	34 (68)
	No	16 (32)
	None	(32)
What is the most uncomfortable sensation?	Burning, numbness or tingling	15 (30)
	Fatigue, cramp or itching	19 (38)
What is the most frequent site of this symptom?	Feet	4 (8)
	Calf	28 (56)
	Others	2 (4)
Is there any time of the day when this (symptom described) increases in intensity?	During the night	11 (22)
	During the day and at night	11 (22)
	Only during the day	12 (24)
Have you ever woken up in the middle of the night because of this symptom?	Yes	18 (36)
	No	16 (32)

Is there anything you can do to relieve this symptom (described)?	Walk	7 (14)
	Stand up	4 (8)
	Sit or lie down	23 (46)

Chi-square test was used to assess a possible association between clinical and angiography signs and peripheral neuropathy, and the presence of dyspnea as an ischemic equivalent symptom was associated with the presence of peripheral neuropathy, as shown in Table 4.

Table 4 – Association between clinical signs of ACS with the degree of peripheral neuropathy. São Paulo, SP, Brazil, 2016

Clinical signs		Degree of peripheral neuropathy				P Value*
		Absent	Mild Neuropathy	Moderate neuropathy	Severe neuropathy	
Precordial pain	Painless	0	0	2	0	0.232
	Catch	10	11	10	2	
	Stabbing	1	1	0	0	
	Burning	5	4	1	3	
Nausea	Yes	8	3	6	1	0.207
	No	8	13	7	4	
Vomiting	Yes	9	3	3	2	0.114
	No	7	13	10	3	
Dyspnea	Yes	3	11	10	2	0.006
	No	13	5	5	3	
Dry cough	Yes	1	0	0	0	0.538
	No	15	16	13	5	
Sweating	Yes	12	12	6	3	0.319
	No	4	4	7	2	

\* Pearson's Chi square test

In the correlation of pain intensity with the score of the NSS, a correlation index of 0.193 was obtained with Pearson's correlation coefficient, indicating that there was no correlation between pain intensity and the score of the Neuropathic Symptom Score (NSS).

Therefore, a high prevalence of peripheral neuropathy was observed in diabetic patients with acute coronary syndrome, but no significant association was observed between the clinical signs of these patients and the presence of peripheral neuropathy (PN), except for dyspnea that was more prevalent in individuals who had some degree of PN.

## ● DISCUSSION

Analysis of data from a population of 50 diabetic patients with Acute Coronary Syndrome admitted to a large university hospital in the city of São Paulo showed that most of this population were male individuals, aged 58-84 years old, with low educational level, corroborating the literature findings that the men with systemic hypertension, dyslipidemia, diabetes mellitus who smoke are at higher risk of cardiovascular complications, e.g. acute myocardial infarction, than women. This was also found in our study<sup>(15)</sup>.

The clinical signs perceived by the participants were precordial pain radiating to the left arm, usually

accompanied by sweating and dyspnea, which is similar to some literature studies<sup>(19)</sup>.

Data from the literature found no significant difference in the clinical presentation of acute coronary syndrome with and without DM. However, some patients with diabetes may develop atypical symptoms such as epigastric pain, syncope and/or dyspnea, and the probable cause of the onset of atypical symptoms is diabetic neuropathy that may reduce the perception of pain due to increased oxidative stress, reduction in nerve growth factors and mitochondrial dysfunction caused by chronic hyperglycemia in these patients<sup>(16,20-22)</sup>.

Precordial pain of 8 point intensity was perceived in 96% of the patients. Although 33 (66%) of the study population had some degree of peripheral neuropathy, no correlation was found between the presence of precordial pain and its intensity with the presence of peripheral neuropathy in diabetics. Corroborating this finding, a study in an emergency room with groups of diabetic and non-diabetic patients demonstrated the similarity between the pain experienced by both groups during acute myocardial infarction<sup>(16)</sup>.

Another study with a population of 3,544 diabetic patients with ACS admitted to an outsourced hospital, found no correlation between absence of pain and diabetes and said that diabetic neuropathy may interfere with pain sensation, but this pain is only observed in patients with advanced neuropathy<sup>(17-18)</sup>. Thus, it can be affirmed that precordial pain was perceived by the participants of this study, although with some degree of peripheral neuropathy.

Just like precordial pain and its intensity, other clinical signs such as ischemic equivalent symptoms showed no significant association with peripheral neuropathy, except for dyspnea, which can be related to delay in seeking emergency medical care.

As it can be seen, data from this and other studies that analyzed the degree of peripheral neuropathy and the intensity of the clinical signs of ACS showed low association when peripheral neuropathy was low or moderate. So, rigorous screening of patients with suspected ACS who have diabetes mellitus as a comorbidity is of utmost importance, because some of these patients may present atypical signs of SCA secondary to severe PN, resulting in delayed emergency care and increased mortality rates<sup>(23-24)</sup>.

Several studies include a list of questions to be posed to patients with suspected ACS, such as type of pain, precipitating factors, site and radiation of pain, quality, intensity, duration, improvement factors and associated symptoms. These questions can be incorporated into the assessment of the degree of peripheral neuropathy in diabetic patients with high index of suspicion of ACS, when these patients have atypical signals, in order to prevent delay in treatment<sup>(24)</sup>.

Assessment of the presence of PN when atypical clinical signs are detected and there is strong suspicion of ACS in DM patients can assist nurses in their decision making and in the implementation of nursing interventions, such as bed rest, non-invasive cardiovascular monitoring including continuous monitoring of blood pressure and heart rate, EEG and collection tubes in cardiac biomarkers.

One limitation of this study concerns the short period of time of data collection. Thus, we suggest further studies with samples based on statistical calculations to allow the generalizability of the results.

## ● CONCLUSION

The present study showed that diabetic patients with ACS have clinical signs similar to those identified in the literature, such as precordial pain (stitching pain) accompanied by sweating, dyspnea, nausea and vomiting, and that most participants had a certain degree of peripheral neuropathy, particularly mild and moderate neuropathy.

The presence and intensity of precordial pain and the frequency of ischemic equivalent symptoms were not related to the degree of peripheral neuropathy, except for dyspnea. However, it is worth emphasizing that this association is greater when the level of neuropathy is severe. So, further signs and symptoms should be detected in this population to help determine if an individual has a cardiovascular disease.

It can be affirmed that delay in the diagnosis of diabetes mellitus and the poor control of labile diabetes mellitus increase the risk for developing cardiovascular events, as well as the probability of peripheral neuropathy.

Therefore, thorough assessment of diabetic patients is necessary, and other assessment tools should be implemented, in addition to the essential semiological scores, especially for patients with strong suspicion of ACS who have atypical symptoms. Assessment of the degree of peripheral neuropathy can be used in these patients.

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