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Case Report

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Multivessel coronary artery disease, angioplasty and endothelial dysfunction in diabetes mellitus. Case Report

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Acronyms
CABG: coronary artery bypass graft
DM: diabetes mellitus
ED: endothelial dysfunction
HT: hypertension
LMCA: left main coronary artery
PCI: percutaneous coronary intervention

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ABSTRACT
Coronary heart disease is the leading cause of morbidity and mortality in patients with diabetes mellitus, and causes changes in the endothelium and vascular smooth muscle. This endothelial dysfunction is a precursor of atherogenic lesions. This article describes the case of a diabetic patient with left main trunk disease who was successfully treated with percutaneous coronary intervention and showed rapid progression of atherosclerotic disease in other vessels, so she needed new percutaneous revascularization. Angiographic images are presented and aspects of endothelial dysfunction in diabetes mellitus and its percutaneous treatment are commented. It is important to early identify and treat endothelial dysfunction in diabetic patients. The choice of the revascularization method should be individualized.
Key words: Diabetes mellitus, Endothelial dysfunction, Multivessel coronary artery disease, Coronary angioplasty

Enfermedad coronaria multivaso, disfunción endotelial y angioplastia en la diabetes mellitus. A propósito de un caso

RESUMEN
La enfermedad coronaria es la principal causa de morbilidad y mortalidad en los pacientes con diabetes mellitus, la cual produce alteraciones en el endotelio y en el músculo liso vascular. Esta disfunción endotelial es precursora de lesiones ateroge-nicas. En este artículo se presenta el caso de una paciente diabética con enfermedad de tronco que fue tratada con éxito mediante intervencionismo coronario percutáneo y presentó progresión rápida de la enfermedad aterosclerótica en otros vasos, por lo que necesitó nueva revascularización percutánea. Se presentan las imágenes angio-gráficas y se comentan aspectos de la disfunción endotelial en la diabetes mellitus y su tratamiento percutáneo. Es importante identificar y tratar la disfunción endotelial tempranamente en los pacientes diabéticos. La elección del método de revasculari-zación debe ser individualizado.
Palabras clave: Diabetes mellitus, Disfunción endotelial, Enfermedad coronaria multi-vaso, Angioplastia coronaria

INTRODUCTION

Coronary heart disease is the most common single cause of death worldwide. More than 7 million people die each year as a result of ischemic heart disease, which corresponds to 12.8 % of all deaths[1].

This disease is the main cause of morbidity and mortality in patients with diabetes mellitus (DM). In the United States about one and half million coronary interventions are performed annually between coronary artery bypass graft surgeries (CABG) and percutaneous coronary intervention (PCI), and it is estimated that 25% of these patients are diabetics. Due to the impact of DM on the cardiovascular system, this population requires not only specific treatment for diabetes as the underlying disease, but also for the associated ischemic heart disease[2].

This article describes the case of a diabetic patient who was successfully treated with PCI, and fundamental aspects of the literature about it are discussed.

CASE REPORT

69-year-old woman, ex-smoker (smoked for about 40 years, one pack per day), with a history of hypertension (HT) for 25 years, treated with enalapril and chlorthalidone, and non-insulin dependent DM for 15 years, treated 2 daily tablets of metformin.

She seeks medical care foreasy fatigue and oppressive pain in the neck on physical exertion.

Her BMI was 29.6 kg/m^2 and the tests performed showed cholesterol 6.74 mmol/L, Triglycerides 3.09 mmol/L, glucose 8.74 mmol/L and creatinine 91 mmol/L.

The baseline 12-lead electrocardiogram showed a flattened T wave in V_1-V_6. Coronary angiography was performed in the Catheterization Laboratory of Hermanos Ameijeiras Hospital (**Figure 1**), where a stenosis of 85 % in the body of the left main coronary artery (LMCA), and an injury of 50 % in the proximal portion of the first obtuse margin were found; the rest of the vessels had no significant lesions.

After dilation of the LMCA lesion, a drug eluting stent was placed in the body of LMCA. Right radial approach was used, and an angiographic (**Figure 1**), clinical and procedural success was achieved.

The patient was discharged 24 hours after the procedure, with the following treatment: aspirin, clopidogrel (dual antiplatelet therapy for 1 year), atorvastatin, enalapril, atenolol and chlorthalidone.

At 5 months the patient reports oppressive chest pain that lasts about 5 minutes and is relieved by sublingual nitroglycerin. She is interviewed and little metabolic control and non-compliance with treatment are found. Another coronary angiography (**Figure 2**) is performed, which confirms the success of the stent implanted in the LMCA and the progression of atherosclerotic disease, as there were lesions of 80 % in the circumflex and obtuse marginal arteries. The non-

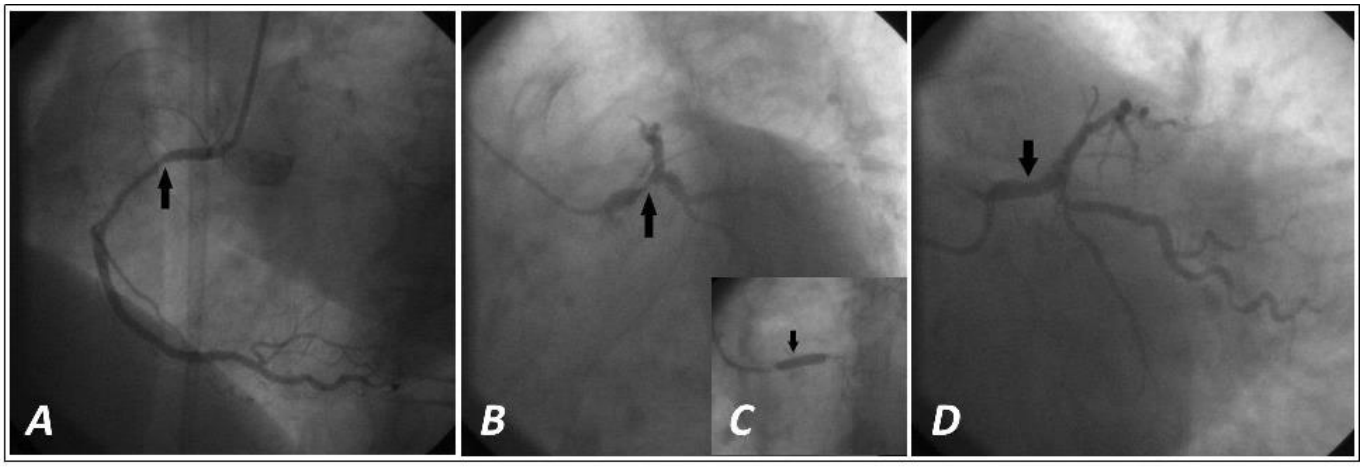

Figura 1. Coronary angiography and PTCA. **A**. No significant lesion in RC (arrow). Left anterior oblique view. **B**. Severe LMCA lesion (arrow). Left anterior oblique view with caudal angulation. **C**. PTCA of the LMCA (arrow indicates the time of stent implantation). **D**. Outcome of the procedure.

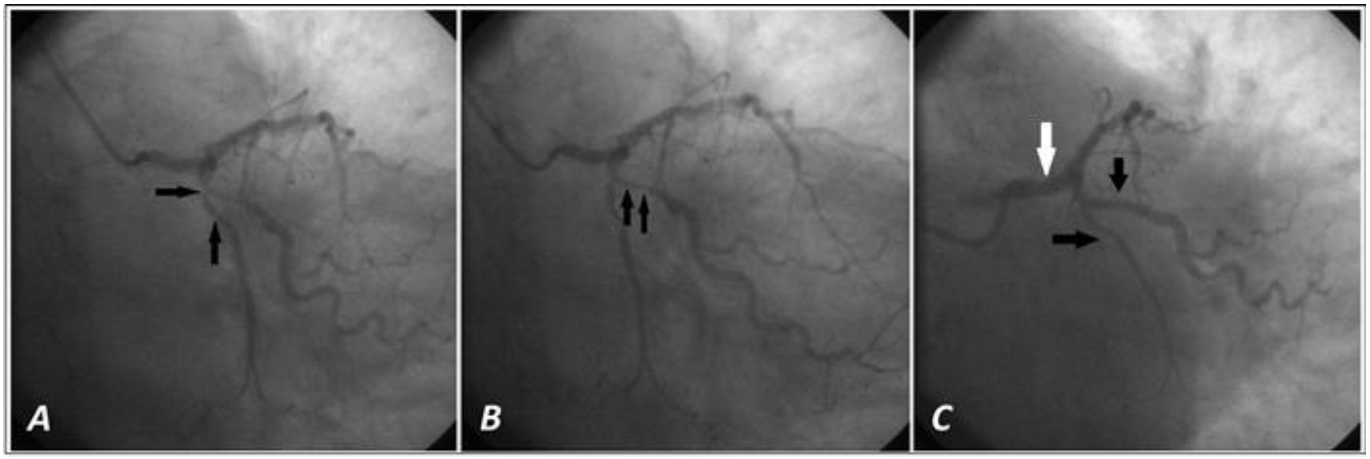

Figura 2. Coronary angiography and PTCA at 5 months. **A and B**. Progression of atherosclerotic disease in Cx and MO (arrows). Left anterior oblique view. **C.** PTCA with stenting of both vessels (black arrows). Persistence of the success of the implanted stent in the LMCA (white arrow).

significant lesion of the right coronary remained unchanged.

PCI was performed with conventional stents in both lesions (**Figure 2**), drug treatment was maintained and stress was made onadjusting metabolic control and starting a cardiac rehabilitation program.

At 7 months the patient remained asymptomatic with good metabolic control and doing rehabilitation. Follow-up coronary angiography (**Figure 3**) was performed according to the protocol of the Center for LMCA disease and the success of all implanted stents was demonstrated, with no other abnormalities.

COMMENTS

DM produces changes in the endothelium and vascular smooth muscle, platelet dysfunction, vasoconstriction and proliferative response at sites of injury[3]. The vascular endothelium should not be considered as the passive coating interposed between the blood and the vascular tree, but as a very large organ of the

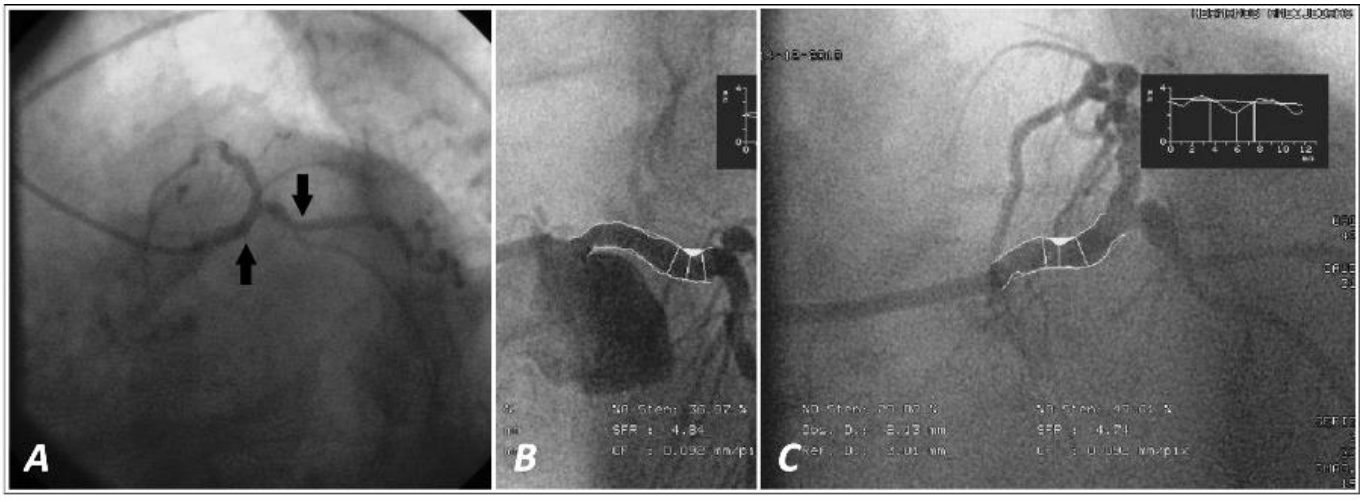

Figura 3. Angiographic control at 7 months of the second procedure. **A**. Persists success of all stents (arrows). **B and C**. Digital angiographic quantification in LMCA.

human body, which fulfills important and dissimilar functions[4-5].

The endothelium-derived nitric oxide is the most important natural vasodilator compound in the body[5-7]. Another substance produced by endothelial cells is prostacyclin that causes relaxation of vascular smooth muscle, and, conversely, also synthesizes vasoconstrictor molecules such as angiotensin II, endothelin-1 and thromboxane A_2, which oppose the vasorelaxing action of nitric oxide, and also promote platelet aggregation and proliferation of smooth muscle cells[6-9].

Thrombomodulin is also produced in the endothelium, and is a tissue activator of plasminogen and glycosaminoglycan of heparan sulfate type, which ensures a normal hemorheology (a concept that includes, among other things, the ability to keep the blood in liquid state even when it has a long contact with the vessel wall) and, with the opposite effects, thrombogenic substances such as the inhibitor of tissue plasminogen activator, tumor necrosis factor alpha, interleukin-1 , and the tissue factor[4-6,8].

Endothelial dysfunction (ED)

It can be defined as the number of conditions affecting the synthesis, release, diffusion, or degradation of factors synthesized by the endothelium. In another definition ED is recognized as the endothelium's loss of the ability to modulate physiological functions of the vascular bed. ED is not homogeneous in its characteristics anddistribution; these aspects vary depending on the diseasethat is present, and the affected vascular bed. Among the triggering mechanisms of vascular damage, and consequently, of ED and diseases that are associated with its appearance are: oxidative stress, hyperhomocysteinemia, dyslipidemia, hypertension, obesity, hyperinsulinemia and diabetes. Meanwhile, ED has been detected in virtually all vascular diseases and occurs in many cases, even before the clinical symptoms appear[5,8,10-12].

Endothelial dysfunction and diabetes mellitus

Chronic hyperglycemia is associated with increased formation of advanced glycosylation products and hyperactivity of aldose reductase-protein kinase C complex, which leads, by complex mechanisms, to an increased oxidative stress, a phenomenon that is closely linked to the occurrence of ED in individuals with DM[13,14].

ED is an early event in the course of type 2 diabetes, there is even evidence that ED markers are elevated in this type of diabetic patients, years before the disease manifests clinically. It is known thatin type 2 DM, in addition to hyperglycemia, the onset of ED is also influenced by insulin resistance and the resulting hyperinsulinemia[13,14]. Meanwhile, 60 % of individuals with type 2 diabetes are hypertensive and 90% obese.

The most common cause of death among European adults with diabetes is coronary artery disease. Several studies have shown that this group has a risk 2 to 3 times higher than people without diabetes[15], diabetic subjects die 10-15 years earlier than those belonging to the general population, and especially due to vascular diseases; besides it has been demonstrated that a diabetic patient has the same risk of having a heart attack, than an individual who has had a first coronary event[16-18].

ED Markers in DM

In DM, the synthesis of nitric oxide, its bioavailability and viability, as well as the relaxing response of the endothelium are affected[19,20].

It has been demonstrated that glycosylated hemoglobin is not only an assessor of metabolic control, but it may also participate in the genesis of the ED. Elevated glycated hemoglobin circulating freely in the plasma, can induce the reduction of nitric oxide-mediated relaxation through the generation of superoxide radicals[20-22].

Another elevated marker of ED in diabetic individuals is endothelin-1. Its increase is considered to be related to the onset of hypertension and the earlier and more severe atherosclerosis, which usually accompanies DM, especially type 2[44-7].

Diabetic dyslipidemia and ED

Diabetic dyslipidemia is characterized by moderate hypertriglyceridemia, decreased high density lipoproteins and presence of small and dense low density lipoproteins, which are very atherogenic, and if total

cholesterol is usually normal, elevated blood concentration that have no clinical impact in subjects without DM, do increase2-3 times cardiovascular risk in diabetic patients[22,23].

Hypertriglyceridemia is currently regarded as a predictor of cardiovascular disease, and the elevation in the plasma of triglyceride-rich lipoproteins in diabetic subjects has been related to the severity of coronary atherosclerosis, which is very often seen in these patients[24]. It is known that triglyceride-dependent lipoprotein diabetic disorders, are magnified in the postprandial state, and are also associated with the onset of ED and ischemic heart disease, hence the importance of postprandial lipid study in diabetics. Insulin resistance is probably the core of the pathophysiological mechanisms of diabetic dyslipidemia[25-27].

Hypertension, obesity, DM and ED

The prevalence of hypertension in diabetics is about twice that in the non-diabetic population, and when hypertension is not controlled, the risk of coronary heart disease doubles [28-30].

It is postulated, from the pathophysiological point of view, that in the absence of renal dysfunction, insulin resistance and compensatory hyperinsulinemia are central in the pathogenesis of hypertension in DM, although it is known to be multifactorial[29].

Obesity, frequently associated with type 2 diabetes (diabesity) and insulin resistance, has been related with increased frequency of coronary artery disease in type 2 diabetics. In obese diabetics increased levels of E -selectin, endothelin-1, resistin, leptin, and resistance to the action of this peptide hormone has been found, as well as a decrease of adiponectin, leptin-dependent nitric oxide production and endothelium-dependent vasodilation[29,30].

Arguably, in individuals with diabetes all vascular diseases related to the atherosclerotic phenomenon occur more frequentlyand it is known that ED is significantly associated with the development of atherosclerosis[31,32].

Treatment of ED in DM

There is evidence to support the conclusion that the best therapeutic measure to prevent the onset of ED or reduce its adverse effects in diabetics, is to achieve an optimal metabolic control[33,34], with or without drug treatment.

There is considerable controversy regarding the usefulness of antioxidant compounds in diseases, including DM, in which the presence of increased oxidative stress and decreased antioxidant defenses has been demonstrated. However, multiple antioxidant compounds have been used to treat oxidative stress and ED associated with DM[31-34].

Treatment of atherosclerotic lesions in diabetics

Autopsy data show that coronary atherosclerosis in diabetics is more severe, with involvement of a greater number of vessels, a more diffuse distribution and a greater number of complicated, ulcerated plaques and with thrombus than in the non-diabetic population[35]. Angiographic studies confirm more severe and diffuse lesions, both proximal and distal, less collateral circulation and increased presence of risk plaques. Diabetics show a faster growth of the lesions when repeated studies in the same patient are compared. New exploration intracoronary procedures (intravascular ultrasound and optical coherence tomography) confirm the presence of a greater number of hot plaques and higher complication rate. As in the case presented, the response of coronary vessels to interventional procedures is less favorable[35,36].

Several studies[37-41] have shown that optimal medical therapy is as effective as CABG or PCI in patients with chronic stable angina and mild heart disease. While these procedures in patients with moderate or severe coronary disease, combined with optimal medical treatment, produce longer survival and better symptomatic relief than medical treatment alone.

Review of comparative trials

In the subgroup analysis of ERACI-II and ARTS trials, diabetic patients treated with CABG had better outcomes than those in the angioplasty group. It was also noted that patients undergoing PCI had less need for repeat revascularization and a lower incidence of serious cardiac complications than surgical patients (71 % vs. 92 % , respectively , and 65 % versus 76 % , respectively). Interestingly, the seven institutions that

participated in the study had an average annual volume of only 57 CABG and use of thebridge with internal mammary artery was only 89%, both percentages are modest by today's standards and may have contributed to increased mortality at 30 days[42,45].

The CARDia[46] trial aims at comparing coronary angioplasty with stent implantation and cardiac surgery in diabetic patients with symptomatic multivessel coronary disease. 510 diabetic patients with multivessel disease or single vessel disease but with great complexity were included and randomized to CABG or ICP (initially with metal and then with drug-eluting stents), and routine use of abciximab. The primary endpoint was a composite of death from any cause, myocardial infarction and stroke; and the secondary endpoint, the combination of the primary endpoint and the need for repeat revascularization. A non-inferiority design was used, so that to consider angioplasty not inferior to surgery, the upper limit of the confidence interval of 95% (95 % CI) had to be less than 1.3[46].

After a year of follow-up, the primary endpoint was achieved in 15% of the surgical group and 13% in the PCI group. The total mortality rates were equal and the combination of death, myocardial infarction, stroke, or repeat revascularization (secondary endpoint) was 11.3 and 19.3 %. When surgical patients were compared with the subgroup of patients who received drug-eluting stents (69% of total), the primary endpoint was achieved in 12.4 and 11.6 %, respectively[46,47].

Their results at one year indicated that although angioplasty is a technique that can be performed safely in these patients, in the long term noninferiority has not been demonstrated. Regarding the secondary endpoint, surgery is significantly better, especially at the expense of a reduced need for repeat revascularization. Regarding the primary endpoint, the upper limit of 95 % exceeds the limit determined for non-inferiority both in the overall group and also if only patients treated with new-generation drug-eluting stents are considered[46,47].

Dr. Eric Bates (University of Michigan, Ann Arbor), in his comments to the articles of Farkouh[48] and Hlatky[49] told Heartwire[50]that if the clinical trial and the previously published evidence are strictly analyzed, FREEDOM supports the superiority of CABG with respect to ICP[50]. However, he noted that from the clinical practice point of view many interventionists can identify patients with high and low risk, and therefore direct them to the most appropriate revascularization treatment. For this reason, some data of registries have shown that clinical events were similar in diabetics undergoing CABG or PCI[48-50].

«It's not PCI vs CABG», said Bates[50]. «These are complementary revascularization procedures, and these trials show that CABG should be an important part of the discussion, but on an individual patient level, there are factors such as the risk of stroke, frailty, renal function, pulmonary function, patient preference, operator experience, and other variables that go into making an individualized patient decision».

FINAL CONSIDERATIONS

ED occurs frequently in subjects with DM, it can even be detected in some of these individuals at the beginning of the metabolic disease. In diabetics, chronic hyperglycemia and the frequent presence of comorbidities associated with DM, favor the development of ED, its presence shows that there are metabolic conditions for the occurrence of diabetic microangiopathy and macroangiopathy (atherosclerosis). As for treatment, several drug and non-drug therapeutic measures are known to have an endothelial anti-dysfunction action, and among the latter it is essential to reach optimal metabolic control.

In cases when myocardial revascularization is decided, evidence points to the surgical treatment of diabetic patients with multivessel coronary disease; although ICP is still an option for patients with specific contraindications to surgery. And both methods should be seen as complementary revascularization procedures.

In this case treatment was performed with ICP and an angiographic, clinical and procedural success was achieved.

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