Dra. Elena Rodríguez González.
Specialist Physician, Non-Invasive Cardiology Unit.
Hospital Universitario Gregorio Marañón (Madrid, Spain).

Atherosclerosis and Coronary Artery Disease in Diabetes

Diabetes mellitus is a disease with a significant socio-health impact, not only due to its high prevalence but also because of the chronic complications it causes and its high mortality rate. Diabetes substantially increases the risk of cardiovascular morbidity and mortality, and it's strongly associated with macrovascular complications such as ischemic heart disease, cerebrovascular disease, and peripheral arterial disease.

Coronary atherosclerosis is the most common form of cardiovascular disease. It is a **chronic inflammatory disease** of the large arteries, specifically affecting the innermost layer, or intimal layer, of the artery wall.

Traditional risk factors like hypercholesterolemia, hypertension, diabetes, and smoking act as powerful pro-inflammatory stimuli. They can disrupt the normal function of the vascular wall, facilitating the accumulation of fat and inflammatory cells within the arterial wall.

Oxidized low-density lipoprotein cholesterol (LDLc), which accumulates in the subendothelial space, is the initial aggressor that triggers the inflammatory reaction. This inflammation plays a role at various levels of the atherosclerotic process: endothelial activation and recruitment of lymphocytes and monocytes, local and systemic production of pro-inflammatory cytokines, degradation of fibrous cap proteins and plaque destabilization, induction of plaque cell apoptosis, and formation of the procoagulant lipid core (1). Diabetes can exacerbate atherosclerosis by amplifying each of these stages.

The metabolic disorders characteristic of diabetes, such as hyperglycemia or the accumulation of advanced glycation end-products, contribute to endothelial dysfunction and an increased vascular inflammatory response. Platelet functions are abnormal in individuals with diabetes, leading to greater production of prothrombotic factors. In addition to accelerating the atheromatous process that leads to the development of atherosclerotic lesions, diabetes promotes plaque instability and triggers clinical events. Atheromatous plaques in people with diabetes are more inflammatory than those in non-diabetics and contain a larger lipid core, associated with a greater number of macrophages and apoptotic smooth muscle cells, which accentuates their **vulnerability** (2).

Coronary artery disease is the leading cause of morbidity and mortality in diabetic patients, who face up to four times higher risk compared to individuals without diabetes. Cardiovascular disease is responsible for most of the increased mortality in patients with type 1 diabetes mellitus and is their primary cause of death after age 30 (3). Ischemic heart disease is the main cause of death in patients with type 2 diabetes mellitus (DM) (4). **Insulin resistance** and the constellation of associated metabolic changes, such as dyslipidemia, hypertension, and obesity, influence the prematurity and severity of atherosclerosis that patients with diabetes mellitus develop. Furthermore, diabetic patients with ischemic heart disease have a worse prognosis with a higher prevalence of ventricular dysfunction and heart failure, often exacerbated by what's known as diabetic cardiomyopathy (5).

Currently, there is strong evidence that immunological and inflammatory mechanisms underlie the development and progression of atherosclerosis (6). Of note, the role that adipose tissue, and therefore obesity, plays in maintaining a chronic inflammatory state.

CLINICAL SIGNS AND DIAGNOSIS OF ATHEROSCLEROTIC CORONARY DISEASE

Atherosclerotic coronary disease often remains a silent condition for many years, causing no limitations or symptoms in the affected person. When atherosclerotic lesions advance, they can grow in volume and significantly narrow the vascular lumen, impeding normal blood flow in the affected coronary artery. Alternatively, they can erode or rupture abruptly, leading to the formation of a thrombus or clot that obstructs the artery lumen, interrupting blood flow and depriving a part of the heart muscle of blood supply. In this way, coronary atherosclerosis can manifest as **stable angina pectoris**, or as unstable angina, **myocardial infarction**, or sudden cardiac death.

The diagnosis of atherosclerotic coronary disease traditionally relied on symptoms, electrocardiograms, stress tests, and occasionally, coronary angiography if clinical suspicion was very high. In the last decade, continuous advancements in computed tomography (CT) have enabled the detection and quantification of atheromatous plaques in the coronary arteries, with sensitivity and specificity practically comparable to data obtained after coronary angiography. **The total coronary artery calcium** (CAC) score, an unequivocal indicator of arteriosclerosis, allows for non-invasive cardiovascular risk stratification with greater reliability than conventional methods.

»

DIABETES SIGNIFICANTLY INCREASES THE RISK OF CARDIOVASCULAR MORBIDITY AND MORTALITY AND IS STRONGLY ASSOCIATED WITH MACROVASCULAR COMPLICATIONS SUCH AS ISCHEMIC HEART DISEASE, CEREBROVASCULAR DISEASE, AND PERIPHERAL ARTERIAL DISEASE

» PREVENTION AND TREATMENT OF CORONARY ATHEROSCLEROSIS

The best treatment for atherosclerotic disease is prevention, acting early on cardiovascular risk factors to prevent or delay the development of lesions as much as possible. Once these are established, there is no specific treatment to eliminate atheromatous plaques. **Statins**, which reduce cholesterol levels, can slow the disease's progression and decrease the risk of rupture or erosion of existing atheroma plaques. Antiplatelet therapy, such as acetylsalicylic acid, is prescribed in some patients to reduce platelet aggregation and lower the risk of thrombosis within the coronary arteries should an athe-

rosclerotic lesion rupture or erode. In patients with severe coronary lesions, in addition to antianginal pharmacological treatment, lesions can be treated with percutaneous coronary intervention or coronary artery bypass grafting in cases of multivessel disease.

In patients with T2DM, recent trials with 2 types of drugs, **sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1a)**, have demonstrated cardiovascular benefits independent of glycemic control and metformin use, leading to new treatment algorithms (7).

In patients with T1DM, **intensive glyce-**

mic control vs conventional treatment was shown to decrease the risk of cardiovascular events by 42% and the probability of non-fatal myocardial infarction, stroke, or death by 57% (8).

Lifestyle interventions are crucial in patients with DM. It's important to maintain a balanced diet low in animal fats, engage in regular physical exercise, avoid overweight, and control modifiable risk factors such as smoking, high cholesterol levels, and elevated blood pressure (7) (see recommendations based on the European Society of Cardiology Guidelines on the management of cardiovascular disease in patients with diabetes in *Table 1*). **D**
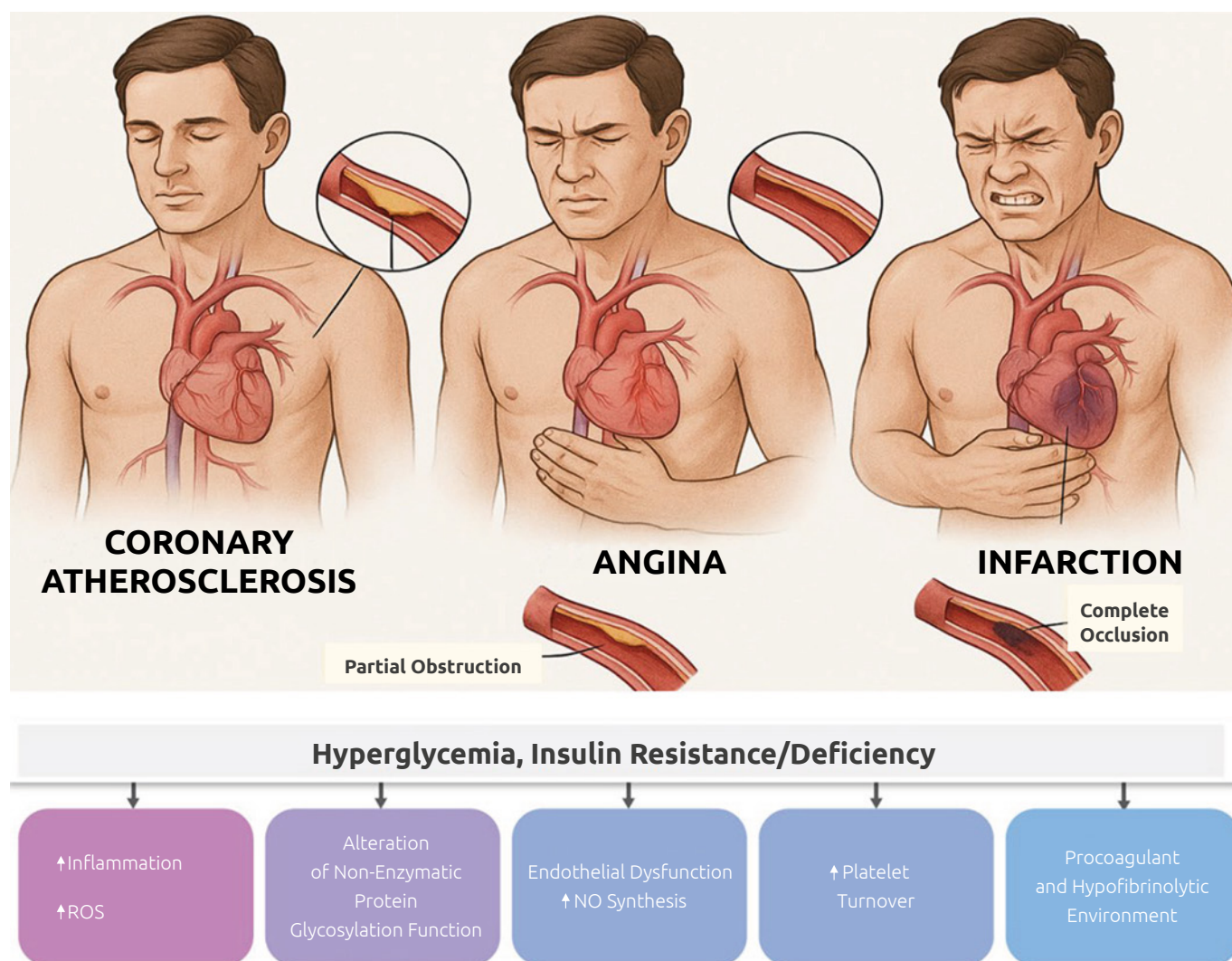
FIGURE 1. Symptoms of coronary artery disease and summary of the pathophysiological mechanisms that accelerate the atherosclerotic process in diabetic patients.

• Adopt a Mediterranean or plant-based diet high in unsaturated fats.
• Smoking cessation is recommended to reduce cardiovascular risk.
• Engage in physical activity. Optimal levels are 150 minutes per week of moderate-intensity activity or 75 minutes of vigorous aerobic exercise.
• Antihypertensive treatment is recommended for all people with diabetes when office BP is ≥ 140/90 mmHg.
• Strict glycemic control (HbA1c < 7%) is recommended, while avoiding hypoglycemia. The HbA1c target should be individualized based on comorbidities, duration of diabetes, and life expectancy.
• An LDL cholesterol target of < 100 mg/dL is recommended for patients with moderate CV risk. For diabetic patients with high and very high CV risk, the targets are < 70 mg/dL and < 55 mg/dL, respectively.
BP: Blood Pressure, HbA1c: Glycosylated Hemoglobin, CV: Cardiovascular.

TABLE 1. Recommendations for Lifestyle and Cardiovascular Risk Management in Patients with Diabetes

CONCLUSIONS

• Coronary atherosclerosis is a chronic inflammatory disease affecting the arterial intima, most commonly manifesting as angina pectoris and acute myocardial infarction, though it can remain silent for many years.

• Cardiovascular disease is the leading cause of death in patients with diabetes mellitus.

• In addition to adequate glycemic control, strict management of other cardiovascular risk factors is essential to prevent the worsening of coronary atherosclerotic disease. This is achieved through healthy lifestyle habits and pharmacological treatment when indicated.

REFERENCES

1. Ross R and Agius L. The process of atherogenesis--cellular and molecular interaction: from experimental animal models to humans. Diabetologia. 1992;35 Suppl 2:S34-40.
2. Moreno PR, Murcia AM, Palacios IF, Leon MN, Bernardi VH, Fuster V and Fallon JT. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. Circulation. 2000;102:2180-4.
3. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z and Keen H. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabet Med. 1999;16:466-71.
4. Stamler J, Vaccaro O, Neaton JD and Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16:434-44.
5. Pop-Busui R, Januzzi JL, Bruemmer D, Butalia S, Green JB, Horton WB, Knight C, Levi M, Rasouli N and Richardson CR. Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association. Diabetes Care. 2022;45:1670-1690.
6. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340:115-26.
7. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, Christodorescu RM, Crawford C, Di Angelantonio E, Eliasson B, Espinola-Klein C, Fauchier L, Halle M, Herrington WG, Kautzky-Willer A, Lambrinou E, Lesiak M, Lettino M, McGuire DK, Mullens W, Rocca B and Sattar N. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023;44:4043-4140.
8. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P and Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53.