Preventing cardiovascular events in diabetic patients: the case of the patient with poor distal coronary targets

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Abstract
Cardiovascular disease is a major cause of morbidity and mortality in diabetes. Hypoglycemia, a common side effect of antidiabetic therapy, is associated with an increased risk for cardiovascular disease in diabetic patients and may precipitate angina in those with underlying myocardial ischemia. Thus, the prevention and prompt recognition of hypoglycemia is highly desirable in diabetic patients, especially in those with ischemic heart disease. Moreover, ischemia due to microvascular dysfunction is a frequent finding in people with diabetes. In that setting, in which surgical or percutaneous coronary intervention are not viable options, a rational use of antianginal therapy may help maximize the cardiometabolic benefits of treatment and improve quality of life. For example, trimetazidine can significantly ameliorate recurrent ischemia with a neutral or even favorable impact on glucose metabolism in diabetic patients. We present a clinical case that illustrates the importance and usefulness of a multidisciplinary approach when treating diabetic patients with ischemic cardiac disease. 

Keywords: coronary artery disease; diabetes; glucagon-like peptide-1 agonists; hypoglycemia; incretin; microvascular coronary dysfunction

Up to 80% of diabetic patients die from cardiovascular (CV) disease. Multiple factors (eg, hyperglycemia, a high level of low-density lipoprotein (LDL) cholesterol, elevated blood pressure, and smoking) contribute to accelerate atherosclerosis. Yet, even after adjustment for all these factors, the relative risk of cardiac mortality remains 3 to 5 times higher in diabetics. For whatever reason, the atherosclerotic involvement in diabetic subjects tends to be more severe and more diffuse than in nondiabetic subjects. Hyperglycemia, per se, exerts a deleterious effect on endothelial function and reduces coronary flow reserve beginning in the early stages of the disease. Studies on heart microcirculatory dysfunction in diabetes suggest that microvascular disease is systemic, occurring in the heart as well, where it contributes to poorer outcome upon coronary revascularization and more common heart failure.
Miss AR is a 63-year-old diabetic woman who was referred to our diabetes center in March 2014. Her family history was positive for coronary artery disease (CAD). She quit smoking in 1993. Her medical history was significant for hypertension, hypercholesterolemia, and obesity. She had type 2 diabetes mellitus (T2DM) for 13 years, complicated by nonproliferative retinopathy, but had preserved renal function and no signs of neuropathy. She was on olmesartan, aspirin, metformin, glibenclamide, and rosuvastatin. Her weight was 86 kg (body mass index, 30.5 kg/m²). Physical examination, blood pressure (135/80 mm Hg), and heart rate (70 bpm) were normal. Her fasting plasma glucose value was 5.5 mmol/L (99 mg/dL), glycated hemoglobin A₁c (HbA₁c) was 54 mmol/mol (7.1%), and LDL-cholesterol was 2.77 mmol/L (107 mg/dL). She complained of bouts of palpitations, confusion, and chest discomfort that usually resolved with ingestion of carbohydrates. Examination of her blood glucose monitoring revealed multiple values <3.9 mmol/L (70 mg/dL), particularly at times of unpredicted physical activity. Because of recurrent hypoglycemic episodes and obesity, glibenclamide was withdrawn and liraglutide initiated at the dose of 0.6 mg daily, to be increased to 1.2 mg 10 days later. A cardiologic evaluation was also planned. Basal electrocardiogram (ECG) analysis (Figure 1) showed signs of altered reperfusion and a dipyridamole stress test was performed, which showed no signs of inducible myocardial ischemia. The rosuvastatin dose was increased to ensure attainment of target LDL cholesterol levels.

Six months later, her HbA₁c level was 47 mmol/mol (6.7%) with a 3-kg loss in body weight and no further episodes of hypoglycemia, though she still experienced chest discomfort during occasions of physical effort-associated dyspnea, which resolved spontaneously within 10 minutes. She underwent myocardial perfusion single-photon emission computed tomography (SPECT) (Figure 2), showing stress-inducible impairment of coronary blood flow reserve, whereas coronary angiography did not indicate significant epicardial coronary artery stenosis. Diltiazem was prescribed to which trimetazidine was then added with marked improvement.

**Discussion**

CAD is common in T2DM patients due to the concomitance of multiple CV risk factors. The role of gly-
Glycemic control on CV risk is a matter of debate. While an association was reported in epidemiological studies, intervention to ensure strict glycemic control has lead to either no effect or a marginal one. Nonetheless, glycemic control remains key to reduce the risk of microvascular complications. Near normal HbaA1c is recommended in patients with a long life expectancy, free of or with mild diabetes complications, as was the case of our patient who had nonproliferative retinopathy and no other microvascular complications. Yet, Miss AR had signs and symptoms of ischemic heart disease in spite of a minor involvement of coronary arteries. This situation may be accounted for by microvascular involvement of the myocardial vascular bed, supporting the need for strict glycemic control. However, treatment should avoid hypoglycemia, which may have been a triggering factor for angina episodes in our patient.

Hypoglycemia is associated with an increased risk for CV diseases. Several mechanisms can contribute to hypoglycemia-induced myocardial ischemia, including QT-interval elongation, hypokalemia, catecholamine discharge, platelet activation, and increased blood viscosity. Though no ECG was recorded during a hypoglycemic episode, it seems reasonable to associate the chest discomfort reported by our patient with a low blood glucose level.

The risk of hypoglycemia is greater with sulfonylureas (especially glibenclamide) than with other oral antidiabetic agents. Moreover, sulfonylureas may worsen the outcome of an ischemic insult because of nonselective interaction with vessel potassium (K+ ) channels and subsequent impairment of posts ischemic preconditioning.

Miss AR was then kept on metformin, but shifted from glibenclamide to liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, without significant hypoglycemic risk, owing to its glucose-dependent effect on insulin secretion and preserved glucagon response to a drop in blood glucose. GLP-1 receptor agonists may also exert extraglycemic effects. Preclinical studies have shown a reduction in the size of the infarct area upon ischemic insult, but there is no evidence that this is the case in diabetic subjects as well. A number of cardiovascular outcome studies employing GLP-1 receptor agonists are currently ongoing. ELIXA (Evaluation of LiXisenatide in Acute coronary syndrome), the first of these trials, shows CV safety of lixisenatide in high-CV-risk patients with a recent acute coronary syndrome episode.

Miss AR was symptomatic and had a positive stress test. Yet no significant coronary stenosis was documented by coronary angiography. This is compatible with heart microvascular dysfunction, a factor sufficient to precipitate myocardial ischemia as well as to impair the outcome of revascularization procedures in the case of CAD. These patients usually benefit from conventional medical therapy. Addition of trimetazidine can help reduce symptoms because of its cardioprotective properties without affecting blood pressure and heart rate. It has been suggested that trimetazidine may exert its antianginal effect by inhibiting fatty acid oxidation and improving glycolysis and glucose oxidation with a neutral or even favorable effect on glucose metabolism.

**Conclusion**

Miss AR’s case should encourage consideration of a “cardiologic” approach in selecting antidiabetic treatment, in order to avoid conditions (eg, hypoglycemia)
that may precipitate CV events, and a “metabolic” approach in selecting CV therapy. Such treatment should have a neutral or even favorable effect on glucose metabolism in diabetic patients with ischemic heart disease.

REFERENCES