Both glucocentric and cardiocentric approaches are necessary for a resilient disease such as diabetes

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Article received: 1/3/2018
Accepted for publication: 1/6/2018

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http://dx.doi.org/10.1590/1806-9282.64.03.212

Summary

Diabetes mellitus (DM) is a complex disease that compromises almost all systems in the organism. Regardless of the intrinsic mechanisms, the cornerstone of all consequences of DM is hyperglycemia, a condition associated with intense metabolic changes leading to increased long-term morbidity and mortality. The introduction of hypoglycemic treatment, mainly insulin and the first oral antidiabetic agents in the first part of the 20th century has changed this scenario, promoting an epidemiologic transition. Indeed, in the second half of the last century, the life expectancy of patients with diabetes increased and cardiovascular-renal diseases became the leading causes of death. As a natural consequence, cardiovascular endpoints became the holy grail in clinical trials with patients with diabetes. The UKPDS trial demonstrated that metformin significantly decreased myocardial infarction rate in patients with diabetes and body weight > 120% of their ideal mass.1 It is important to notice, however, that, in the UKPDS trial, the average LDL-cholesterol level was 141 mg/dL at baseline and remained above the recommended target for this high-risk cardiovascular group after the long-term follow-up suggesting suboptimal cardiovascular risk factors control.1,2

Several different therapeutic hypoglycemic oral agents were developed for the treatment of hyperglycemia acting at different sites. In 2009, a pathophysiological approach was proposed as a new paradigm to achieve durable glycemic control in patients with DM. The new paradigm is based on a creative scheme called the ominous octet that has hyperglycemia in its core.3 According to this algorithm, a triple combination of hypoglycemic drugs should be added to lifestyle intervention targeting HbA1c < 6.0%.

Keywords: Atherosclerosis. Diabetes Mellitus. Risk Factors. Coronary Artery Disease.
The ACCORD trial, however, put a damper on the glucocentric approach and was stopped earlier than anticipated due to higher mortality in patients enrolled in the intensive glycemic control group, without benefit in major cardiovascular events during 3.5 years of follow-up. \(^4\) In addition, concerns rose for the consequences of severe hypoglycemia seen in the UKPDS trial that revealed a two-fold increase in the occurrence of major hypoglycemic events with the use of glibenclamide, a first generation sulphonylurea. \(^5\) The development of second generation sulphonylureas has significantly decreased the occurrence of severe hypoglycemic events. The incidence of severe hypoglycemia in the intensive treatment arm in the ADVANCE trial that included the second generation modified release sulphonylurea gliclazide was 2.7%. \(^6\) Interestingly, in the second 5-year-phase of this study (ADVANCE-ON), the use of oral antidiabetic drugs was at discretion of the attending physician, and the results showed that the mean between-group difference in glycated hemoglobin levels (lower in the intensive arm in the first phase) was no longer evident. Moreover, in spite of the increased glycated hemoglobin levels in both arms in the ADVANCE-ON, the occurrence of severe hypoglycemia was higher, 8.4% on average, suggesting that both safer drugs and closer follow-up care are necessary for DM patients. \(^7\) Unfortunately, optimal glycemic control remains far below desirable rates in recent studies, indicating careless glycemic control, especially for the treatment of older DM patients. \(^8\)

In conclusion, we recognize that severe hypoglycemia is a condition to be absolutely avoided but not at the expense of a lax glycemic control. \(^9\) Both the glucocentric and cardiocentric approaches are necessary for a disease as resilient as diabetes mellitus. In addition, the adequate care of patients with DM must involve early diagnosis of hypoglycemia, the control of cardiovascular risk factors (dyslipidemia and hypertension), as well as the identification of patients with established or high risk for heart failure, a major complication. Considering the worldwide growing number of patients with diabetes, caregivers must follow a dialectical thinking and choose a synthesis approach where glycemic control is as important as control of cardiovascular risk factors and should remain a target to be achieved.

**References**