Av Diabetol. 2011;27(2):39–41

AVANCES EN DIABETOLOGÍA

www.elsevier.es/avdiabetol

EDITORIAL

Hypoglycaemia and cardiovascular disease. The fatal linkage

Hipoglucemia y enfermedad cardiovascular. Una asociación fatal

Cardiovascular disease (CVD) represents the major cause of morbidity and mortality in subjects with both type 2 (T2D) and type 1 diabetes mellitus (T1D).[1-3] Patients with diabetes have a shorter life expectancy when compared with individuals without the disease and this excess mortality is largely due to accelerated atherosclerotic processes.

Hypoglycaemia associated with glucose-lowering therapy represents a significant barrier to successful treatment of diabetes and it causes recurrent morbidity in most people with the disease.[4] Moreover, it is an obstacle to the maintenance of euglycemia over a lifetime and thus precludes euglycemia's long-term benefits.[5] There is no doubt that glucose management, particularly if intensive, is related to an increased risk of non-severe and severe episodes of hypoglycaemia in patients with T1D and this is also the case for patients with T2D, especially in those insulin-treated.[6]

The latest results derived from several recent large randomised clinical trials performed in subjects with T2D aimed to evaluate the effect of improving glycemic control in CVD have raised the cocern that severe hypoglycemia may increase the risk of a poor outcome in patients with T2D assigned to an intensive glucose-lowering intervention. In fact, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was halted due to a significant increase in death and cardiovascular mortality in the intensive treatment arm (from 22 to 35 %).[7] Whichever the arm allocated, intensive or conventional, those patients with severe hypoglycaemia had a higher mortality risk than those without episodes. However, it should be underlined that in a post hoc analysis, the relative risk of death associated with severe hypoglycaemic episodes was higher in the standard arm (2.87) when compared with intensive strategy (1.28) in spite of a larger number of severe hypoglycaemic episodes in the intensive group. Additionally, data analysis from the same study suggested that the excess mortality in the intensive treatment group was not directly explained by the high rate of episodes of hypoglycaemia. In VADT trial (Veterans Affairs Diabetes Trial), an increased incidence of severe hypoglycaemia was also found in the group receiving intensive treatment of hyperglycemia, but at the end of the study there was no significant difference in CVD events between standard and intensive treatment arms.[8] Considering HbA_{1C} goals at the beginning of both studies (more rigorous in VADT) and differences achieved at the end of both trials (– 1.16 and – 1.01, VADT and ACCORD, respectively), more intensive glycaemic control regimen could be the explanation for differences in rates of severe hypoglycaemia (16 and 21%, participants with ≥1 episodes during study; ACCORD and VADT, respectively). In addition to this, participant characteristics at baseline (age, disease duration, HbA_{1C} and history of macrovascular disease) could be also related with the higher rate of episodes of severe hypoglycaemia observed in VADT trial.

In the one of latest analysis of data from the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) the authors also dealt with the relationship between hypoglycaemia and CVD. The results indicated that severe hypoglycaemia was associated with increased risks of microvascular and macrovascular events and death (from both CVD and non CVD causes).[9] However, this association was markedly attenuated after adjustment for different confounding factors. More recently, Johnston et al. using data from healthcare claims for individuals with employer-sponsored primary or Medicare supplemental insurance claimed for an independent association between ICD-9 CM coded outpatient hypoglycaemic episodes and acute cardiovascular events.[10]

Although it could be argued that the association between hypoglycaemia and CVD is because the former is a marker of high risk for adverse clinical outcomes and there is no current full evidence claiming for causality, the total absence of a direct causal link is far from proven. In fact, the response to hypoglycaemia includes direct and indirect changes mainly related to the activation of sympathoadrenal axis (increase in adrenalin and noradrenalin) and counter-regulatory hormonal secretion (glucagon, hypothalamo-pituitary-adrenal-axis) which produces significant changes

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in the cardiovascular system.[11] During acute hypoglycaemia there is a rapid proinflammatory, platelet aggregatory, antifibrinolytic and prothrombotic response, as well as, disturbances in normal endothelial function.[12] There are very recent studies specifically designed to address the effects of acute hypoglycaemia confirming its proinflammatory and prothrombotic effects.[13,14] The vast majority of these abnormalities are interdependent and due to the activation of sympathoadrenal axis. If recurrent, hypoglycemic episodes may provoke changes in hemostatic factors and viscosity; this might reduce perfusion in diabetic microangiopathy. In addition to this, repeated hypoglycaemia throughout life could potentially aggravate atherosclerosis processes and increase the cardiovascular risk, particularly of those most vulnerable subjects.

Normal hemodynamic response to hypoglycemia includes an increase in heart rate, an increase in systolic and a small decrease in diastolic blood pressure which is due to the sympathetic neural activation. There are several reports showing low glucose values causing ST wave changes with QT interval and cardiac repolarization prolongation.[15] Recently, these changes in QT, as well as, rhythm disturbances have been described in response to nocturnal hypoglycemia in ambulant patients with T1D, which may support the idea of an arrhythmic basis for "death in bed syndrome.[16] Moreover, performing 24-hour monitoring of subcutaneous glucose level using continuous glucose monitoring and simultaneous ambulatory blood pressure measurement in a group of patients with T1D and T2D, Feldman-Billard et al. demonstrated a close temporal relationship between low values of glucose measurements and an increase in blood pressure.[17] There are also reports indicating temporal relationship between acute cardiac events (acute coronary syndromes, angina…) and hypoglycaemia.[18] Moreover, the association of a higher mortality rate and hypoglycaemia in critically ill patients has also emerged from large multicenter randomised trials.[19] Although the development of hypoglycaemia in critical illness could be a surrogate marker for severity, it may also contribute to the fatal result.

The relationship between hypoglycaemia and atherosclerosis in T1D subjects has been recently investigated. In comparison with a control group of patients without, subjects with repeated hypoglycaemia displayed impairment in endothelial function and higher values of carotid/femoral intima media thickness.[20] Though preliminary, these results pointed towards repeated hypoglycaemia as an aggravating factor for preclinical atherosclerosis. However, the intrinsic limitations of this type of study do not allow for blaming repeated hypoglycaemia as an independent risk factor for CVD and extrapolate any causal association.

In summary, current available information confirms that non severe and severe hypoglycaemia is a far from uncommon adverse event in T1D and T2D especially in patients under an intensive management of glucose levels. In the short term, hypoglycaemia may precipitate and aggravate a vascular event during an acute episode. In the long term, especially if repeated, it could be related, theoretically, to the induction and progression of atherosclerosis. An association between hypoglycaemia and adverse clinical events, mainly cardiovascular, has been claimed in some studies. However, although direct causality can not be completely excluded, for the moment, current data suggest that hypoglycaemia could merely identify more vulnerable patients. From a practical point of view, it seems essential not only to place glucose within normal values, but also to avoid hypoglycaemia. From the clinical research perspective, specific trials aimed to investigate on mechanisms linking hypoglycaemia and CVD are required.

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Ignacio Conget

Diabetes Unit, Endocrinology Department, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer), Hospital Clínic, Barcelona, Spain

E-mail: iconget@clinic.ub.es