



COMMENT ON KHUNTI ET AL.

## Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care* 2015;38:316–322

Marga Giménez, Antonio J. Amor, Carmen Quirós, and Ignacio Conget

*Diabetes Care* 2015;38:e91 | DOI: 10.2337/dc15-0271

We have read the article by Khunti et al. (1) suggesting that hypoglycemia is associated with an increased risk of cardiovascular (CV) events and all-cause mortality in insulin-treated patients with diabetes.

The authors mentioned in the discussion that several potential mechanisms linking hypoglycemia and CV risk have been proposed. However, in their opinion, these mechanisms are more likely to explain a transient increase in CV risk during the acute episode of hypoglycemia rather than the longer-term relationship observed in their current study.

We addressed the question of whether repeated episodes of hypoglycemia represent an aggravating factor for macrovascular disease in subjects with type 1 diabetes (T1D) in a previous study (2). Subjects with T1D (age  $34.6 \pm 7.8$  years, T1D duration  $16.1 \pm 6.3$  years) using multiple doses of insulin and with an absence of other major CV risk factors and micro/macrovascular complications and no autonomic dysfunction were included. We compared subjects with repeated nonsevere and severe hypoglycemia with an age- and sex-matched control group with T1D presenting  $<2$  nonsevere episodes per week and with no previous episodes of severe hypoglycemia. Flow-mediated dilatation in response to ischemia was significantly reduced in subjects with T1D with repeated episodes of hypoglycemia when compared with those patients

without it. In the case of carotid and femoral territories assessment, it gave significant higher values of intima-media thickness in subjects suffering from repeated hypoglycemia. These observations suggested that in addition to the alterations in endothelial function that occur early in T1D, recurring episodes of hypoglycemia could be considered an aggravating factor for preclinical atherosclerosis. The exposure to a risk factor throughout the life span in young people could promote the accumulation of subclinical atherosclerosis, which will be translated into CV events but not until much later in life.

In our opinion, there are different possible explanations for the putative relationships between hypoglycemia and CV disease. During acute hypoglycemia, there is a rapid proinflammatory, platelet aggregatory, antifibrinolytic, and prothrombotic response, as well as disturbances in normal endothelial function. The vast majority of these abnormalities are interdependent and due to the activation of the sympathoadrenal axis. Then, hypoglycemic episodes may provoke changes in hemostatic factors and viscosity, reducing perfusion in diabetic microangiopathy. Significant higher values of some inflammatory and endothelial dysfunction markers during euglycemia were detected in subjects with a background of repeated hypoglycemia.

Although there is still a lack of information supporting this second hypothesis,

we can speculate a situation where a patient with T1D with repeated and symptomatic hypoglycemic episodes exhibits a progressive damage to the endothelium secondary to all these possible mechanisms. However, if this patient loses his awareness of hypoglycemia after years, his risk for severe hypoglycemia will increase dramatically, while the damage to endothelium will probably be reduced in each of his nonsevere hypoglycemic episodes as the activation of the sympathoadrenal axis will be lower in this situation. This is just speculation and requires further investigation. In the meantime, like the authors, we strongly recommend that severe and repeated hypoglycemia and hypoglycemia unawareness need to be detected, prevented, and avoided using all the strategies available.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

### References

1. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. *Diabetes Care* 2015; 38:316–322
2. Giménez M, Gilabert R, Monteagudo J, et al. Repeated episodes of hypoglycemia as a potential aggravating factor for preclinical atherosclerosis in subjects with type 1 diabetes. *Diabetes Care* 2011;34:198–203

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

Corresponding author: Marga Giménez, [gimenez@clinic.ub.es](mailto:gimenez@clinic.ub.es).

The author(s) of the cited article did not feel a response was needed.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.