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Letter by Fuentes et al Regarding Article, “J-Shaped Association Between Serum Glucose and Functional Outcome in Acute Ischemic Stroke”

To the Editor:

We have read with interest the paper from Ntaios et al reporting the finding of a J-shaped association between admission serum glucose and functional outcome in acute ischemic stroke (IS).1 The majority of studies addressing the role of glucose levels have focused on hyperglycemia upon admission, which is known to be a common complication in IS patients. Less attention has been paid to the development of hypoglycemia in stroke patients. Now, Ntaios et al have demonstrated that admission glucose levels lower than 3.7 mmol/L (63 mg/dL) are also detrimental in acute IS. The next question that should be answered regards the clinical and therapeutic relevance of this finding.

First, we should address the rates of IS patients with admission glucose levels lower than 3.7 mg/dL. In the Ntaios study, only 4 patients of 1446 (0.29%) presented that level of hypoglycemia. In the GLIAS study,2 a prospective and multicenter, observational study conducted in Spain, none of the 476 acute IS patients included had admission glucose levels lower than 4 mmol/L. Thus, this value seems to be of scarce clinical relevance.

Second, as Ntaios et al suggest, their findings are limited by the retrospective approach and by analysis of only admission values, without any data from glucose level monitoring during the first hours after stroke onset. However, they may provide an explanation for the negative results of clinical trials; this is because small reductions in glucose levels would correspond only to a small improvement in outcome, because of the J-shaped relationship. More importantly, in our opinion, is the fact that patients with large reductions in glucose levels could be associated with significantly higher mortality. This fact, which may also be explained by this J-shaped association, raises a question regarding the optimal glucose level range in which we should maintain patients.

Third, it is becoming more evident that glycemia is a dynamic biological parameter, in which nocice effects could persist beyond the first hours after stroke onset. In this sense, the GLIAS study identified glucose levels of 155 mg/dL during the first 48 hours as the threshold for poor outcome;2 more recently, they found that persistent high glucose levels during the first 48 hours were a more powerful predictor of poor outcome than was admission glycemia.3 Thus, additional studies should also be focused on identifying the lower threshold levels for glucose within the first 48 hours for which a higher risk of poor outcome is found. That could help in identifying the optimal glucose range for our IS patients and in designing therapeutic guidelines.

Finally, we agree with Ntaios et al that they have been the first, to our knowledge, to report a J-shaped relationship between glucose levels and stroke outcome. However, they discuss the possible impact of that finding on treatment guidelines, and suggest that values >7.3 mmol/L (133 mg/dL) are those associated with poor outcomes; we would like to remind them that the GLIAS study was the first to our knowledge to identify, in the year 2009, a glucose level threshold for poor outcome, from a prospective and multicenter approach. We reported that hyperglycemia ≥155 mg/dL at any time within the first 48 hours from stroke onset, and not only the isolated value of admission glycemia, was associated with poor outcome independent of stroke severity, infarct volume, diabetes, or age.2 Taking into consideration that Ntaios et al’s study is based on a retrospective analysis of admission glucose levels, data from the GLIAS study should have more weight in the design of new therapeutic studies and also in clinical guidelines.

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