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Effect of Magnesium Loading Dose on Insulin Resistance in Patients With Stress-Induced Hyperglycemia: A Randomized Clinical Trial

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We read with great interest the article of Heidary et al[1] published in this journal. With their research, the authors addressed an important issue by presenting to the best of our knowledge first data on the effects of magnesium on insulin resistance under conditions of stress-induced hyperglycemia in intensive care unit (ICU) patients. With regard to type 2 diabetes mellitus (T2D), there is an ongoing debate on the role of magnesium on related insulin resistance.[2,3] Results from clinical trials investigating the effect of magnesium supplementation on insulin resistance and metabolic control in human T2D are limited and clinical evidence showing a clear benefit is lacking.[3] For critically ill human patients, Heidary et al propose that a single loading dose of 7.5 g of intravenous magnesium sulfate at ICU admission has significant beneficial impact on insulin resistance after 3 days, as assessed by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).[1] However, in our opinion, the results should be interpreted with great caution: HOMA methods are widely accepted and, due to their ease and cost effectiveness, commonly used to estimate insulin resistance.[4] Otherwise, previous studies have shown that within-person coefficients of variance can be 30% or more for the HOMA-IR in mixed collectives as compared to the gold standard measure of in vivo insulin resistance, the hyperinsulinemic euglycemic clamp.[5-7] The short-term repeatability of HOMA-IR (commonly measured within weeks) is poorly studied and shows significant variation.[7] Thereby, variance of fasting insulin was identified as major driver of HOMA-IR variation.[8] In research settings aiming at improving insulin resistance, this phenomenon is of high relevance. For instance, hepatic clearance is one of the main determinants of insulin extraction and therefore of circulating insulin levels.[9] At ICU admission, up to 61% of patients show elevated liver function tests potentially indicating critical illness–related acute liver injury,[10] while at the same time stress-induced hyperglycemia results in hyperinsulinemia.[11] Both reduced clearance and elevated secretion can substantially contribute to fasting insulin variance and therefore significantly impact HOMA-IR measurements. In the study of Heidary et al, alanine aminotransferase levels of the placebo group were more than 2-fold elevated (due to the limited number of included patients yet not significantly) at ICU admission when compared to individuals of the magnesium group.[1] Thus, impaired liver function with reduced insulin clearance and resulting higher circulating levels at admission could have significantly influenced the observed results. Even more problematic is the application of insulin as a treatment option in both groups, while no data on the cumulative insulin application rate are shown, nor on C-peptide levels, with twice as much patients in the magnesium group receiving insulin.[1] Furthermore, systemic inflammation is the main determinant of insulin resistance under conditions of stress-induced hyperglycemia resulting in hyperinsulinemia.[11] In nondiabetic patients, stress-induced insulin resistance is quickly normalized with resolving inflammation. However, while in the study of Heidary et al C-reactive protein levels were comparable between groups at ICU admission, no data are given regarding the course of inflammation on day 2 or 3.[1] Moreover, in spite of their known counterregulatory effects on insulin action,[11] no data on the intensity and duration of catecholamine therapy are provided. Therefore, the presented data

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on blood glucose and HOMA-IR 3 days after magnesium or placebo treatment are barely interpretable for the interested reader. Finally, the absolute difference in HOMA-IR in the study of Heidary et al of −0.11 (−0.19 to −0.01) between groups (although statistically significant)[1] is minor and lays in the range of the coefficient of variance of HOMA-IR.[5-7]

In conclusion, the role of magnesium treatment on acute stress-related insulin resistance is of potential clinical interest. Regarding the significant methodological limitations raised, we believe, however, that the data of Heidary et al potentially overestimate the treatment effect of magnesium. For an appropriate investigation of this issue, administration of the hyperinsulinemic euglycemic clamp method ideally in combination with stable isotope approaches would represent the methodological state of the art, as we have shown under rapid insulin resistance inducing lipid challenge conditions in human adults.[12]

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