Insulin-induced hypoglycemia decreases IGF-1 bioactivity in humans: a missing link to increased mortality in diabetic patients?

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BACKGROUND

The mechanisms underlying the association between severe hypoglycemia and increased cardiovascular mortality among patients with diabetes mellitus are not fully understood. Our aim was to evaluate changes in GH/IGF-1 axis during insulin-induced hypoglycemia, as a possible link.

METHODS

Twenty-five healthy subjects, 12 obese participants (OP; 6/ 6; 34.4 ± 1.7 kg/m2), and 13 healthy lean participants (LP; 6/ 7; 21.7 ± 0.6 kg/m2) were studied using insulin tolerance test and changes in GH, total IGF-1, IGF binding proteins (IGFBPs) and IGF-1 bioactivity, measured by the cell-based KIRA method, were investigated. Moreover, the effect of insulin on mRNA expression of parts of the GH/IGF-1 system was further studied in mouse primary hepatocytes.

RESULTS

Under hypoglycemic conditions, insulin significantly increased IGFBP-2 and decreased IGF-1 bioactivity in both groups ($p<0.01$). This was followed by a surge in growth hormone ($p<0.01$). As expected, insulin decreased IGFBP-1 levels, whereas no changes in total IGF-1 and IGFBP-3 levels were observed. In vitro, insulin stimulation of primary hepatocytes lead to a decrease of IGFBP-1 and IGFBP-3 and increase of IGFBP-2 mRNA expression.

Figure.1

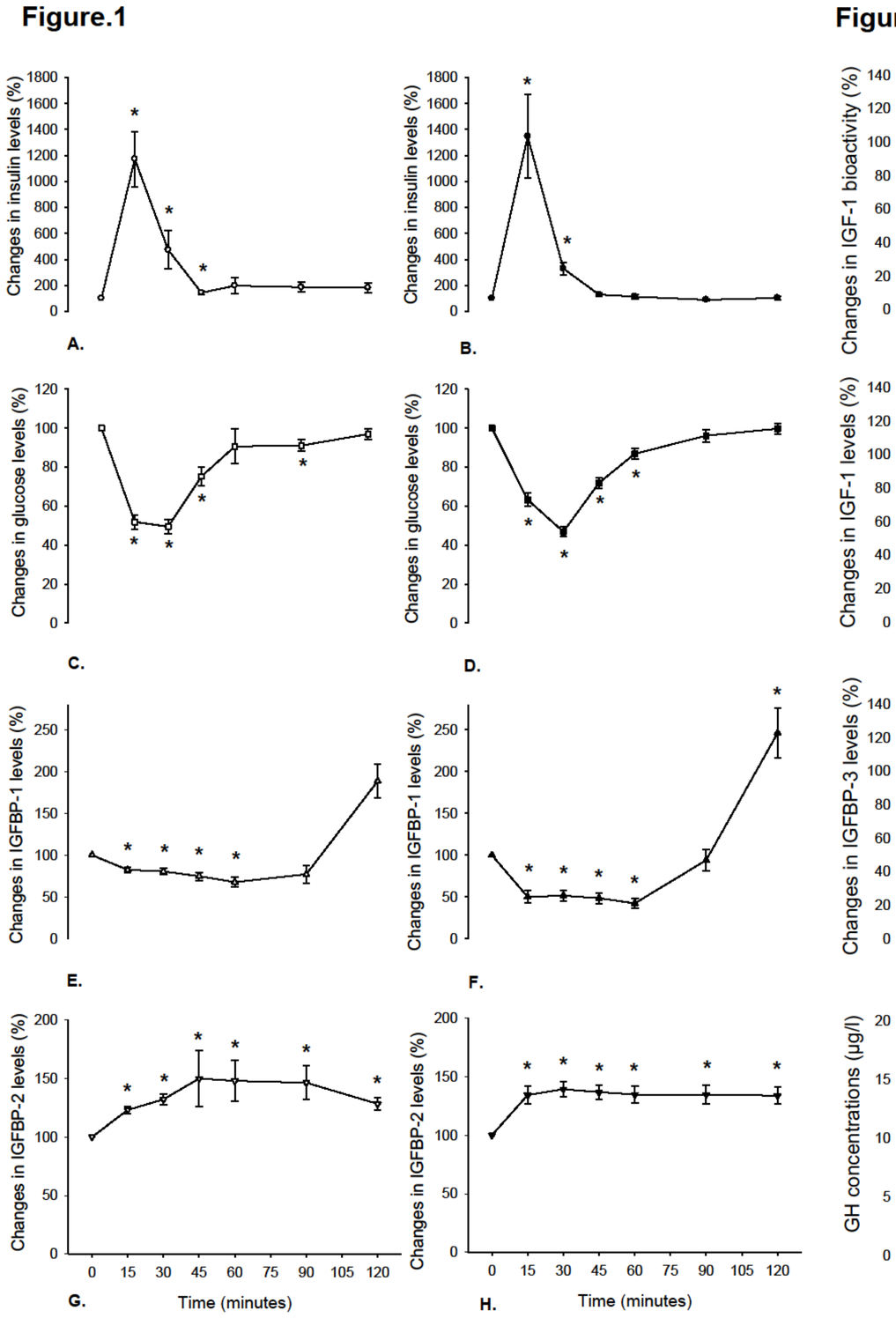


Figure.2

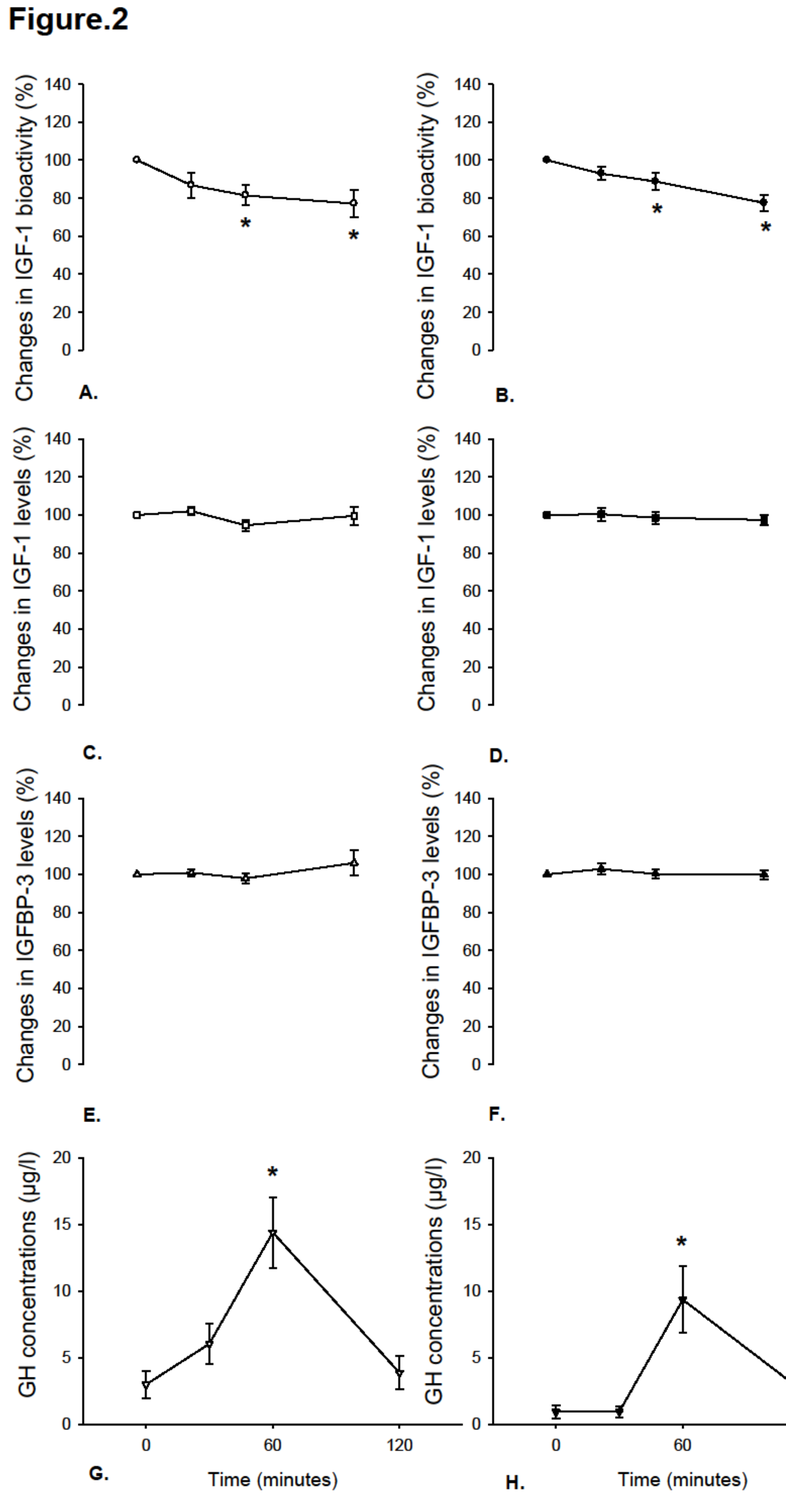
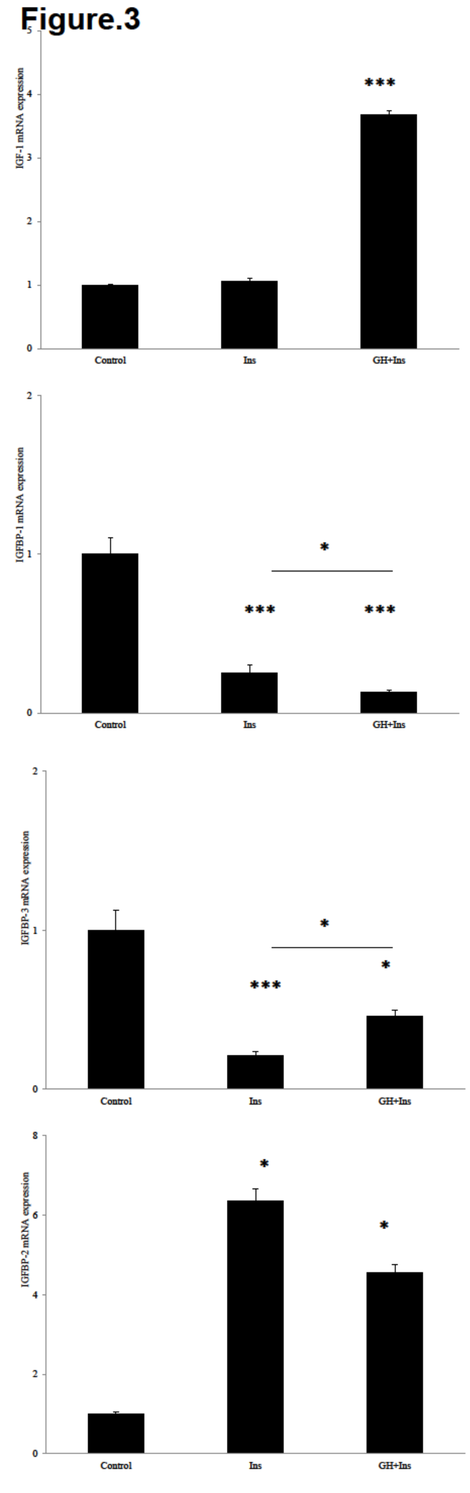


Figure.3



CONCLUSIONS

The insulin-induced hypoglycemia is associated with a decrease in IGF-1 bioactivity through up-regulation of IGFBP-2. Our results point to a possible and previously poorly explored mechanism explaining the strong association between hypoglycemia and increased cardiovascular mortality among diabetic patients

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