Aim: Sunitinib, a VEGFR tyrosine kinase inhibitor (TKI) is registered in metastatic renal cell carcinoma (mRCC), gastrointestinal stromal tumor (GIST) and pancreatic neuroendocrine tumors. In patients with diabetes who were treated with sunitinib, a decrease in blood glucose levels and symptomatic hypoglycemas have been reported. Some preclinical studies suggest that improved insulin sensitivity may be the underlying mechanism. Therefore we studied the early effects of sunitinib on insulin sensitivity and insulin steady-state concentrations.

Methods: In 10 mRCC patients, after an overnight fast, a 120 minutes hyperinsulinemic euglycemic clamp (insulin infusion rate 60 mE.m$^{-2}$.min$^{-1}$; steady state 90-120 minutes) was performed before and one week (7-10 days) after start of sunitinib 50mg per day. Insulin levels were measured using a radio-immune assay. Insulin sensitivity index ($S_i$) was defined as glucose disposal rate normalized for steady state blood glucose concentration divided by the steady-state plasma insulin.

Results: One patient with diabetes (treated with metformin) and 9 patients without diabetes were included in the study protocol (Female/Male: 1/9). Co-medication did not change during the study. The insulin sensitivity index decreased from 0.22 ± 0.04 µmol/kg$^{-1}$.min$^{-1}$. (mE insulin/L)$^{-1}$ before to 0.18 ± 0.02 µmol/kg$^{-1}$.min$^{-1}$. (mE insulin/L)$^{-1}$ (p < 0.05) one week after start of sunitinib. Insulin steady-state concentrations during the clamp increased from 128.9 ± 9.0 mE/L to 170.8 ± 12.8 mE/L (p < 0.05) after one week of sunitinib treatment. Fasting insulin and glucose concentrations did not change.

Conclusions: Sunitinib increased steady-state insulin concentrations by 30% most likely as a result of impaired insulin clearance. In our study group, mostly without diabetes, insulin sensitivity decreased. These alterations were already observed as early as one week on sunitinib treatment. In patients using insulin or insulin-secretion stimulating agents the effect of sunitinib on insulin clearance could result in overexposure to insulin and thereby induce hypoglycemia. Intense blood glucose monitoring in patients with diabetes is therefore essential in the first week after starting sunitinib.

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